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CHEMISTRY OF THE OPIUM ALKALOIDS

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FOREWORD

More than a century has passed since the isolation of crystalline morphine from opium by Sertürner, and during more than half of this period scientific research has been directed toward a solution of the constitutional question of this important alkaloid. The problem may now be regarded as essentially solved, even though some uncertainty still exists concerning the modification of the fundamental formula of Ludwig Knorr which has resulted from the researches of Robinson and of Schöpf. In the case of the less complicated bases which accompany morphine in opium, as papaverine, narcotine, and similar alkaloids, the problem was more rapidly solved. While in these series the structure as determined by analytical procedures has been in nearly every case confirmed by synthesis, the morphine group itself has stubbornly resisted all synthetic efforts.

The alkaloids are treated in chemical monograph literature as stepchildren. If exact information in this field is desired, one must turn to the original literature which is widely scattered in the journals of all lands.

I regard it as a great service by Doctor Small that he has, with unusual effort and care, gathered together the extensive material on the alkaloids of opium and organized it into this excellent monograph. It is intended to be complete. The author writes me, "It is my hope and my belief that every reaction and every compound described in the literature is mentioned," and I believe that this assurance is well founded.

The volume extends far beyond the scope of a mere systematic collection of facts, however, in describing historically the discovery and investigation of each opium alkaloid, and in discussing critically and exhaustively the structural question.

For this timely book I believe great thanks are due to the author, who has himself made valuable experimental contributions to the chemistry of the opium alkaloids. The subject and quality of the contents guarantee that the monograph will have a wide distribution.

The writer takes satisfaction and pleasure in the knowledge that the stimulus which Doctor Small received in the Munich laboratory several years ago has proved to be so fruitful for alkaloid chemistry.

HEINRICH WIELAND.

MUNICH, *May 24, 1931.*

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AUTHOR'S PREFACE

The material presented in this volume has been assembled in the course of a systematic study of the literature of the opium alkaloids, which was undertaken as a part of the alkaloid research project established at the University of Virginia by the Committee on Drug Addiction of the National Research Council with funds supplied by the Bureau of Social Hygiene (Inc.), of New York. The purpose of the book is primarily to make accessible what is known of the chemistry of these alkaloids and their derivatives; hence the history and chemistry of opium is not considered, and no attempt has been made to cover the vast pharmacological literature. In the appendix, addenda have been made from sources which were not available when the book went to press, or from publications which have appeared most recently. The literature to January 1, 1932, has been covered.

In Part I, the benzylisoquinoline and minor alkaloids are considered in separate chapters, each having its own bibliography. In order that the discussion of reactions and structure should not be confused by experimental details, the preparation and properties of derivatives of the individual alkaloids are treated in a descriptive section. Derivatives are arranged in the descriptive part in the same general order as they are discussed in the text, in order that related compounds may be described in sequence. Several alkaloids whose occurrence in *Papaver somniferum* is doubtful (aporeine, rhœadine) have likewise been included for the sake of completeness. The sinomenine alkaloids are mentioned only in those cases where actual conversion to optical antipodes of morphine derivatives has been realized.

The great complexity of the chemistry of the phenanthrene alkaloids, morphine, codeine, and thebaine, which are treated in Part II, has necessitated a considerable division into smaller chapters. This permits a more detailed consideration of important derivatives than would be possible if they were discussed in the sections dealing with the properties and reactions of the parent alkaloids. Each of these subdivisions has its own complete bibliography, wherein the literature relating to that particular field is collected to facilitate specialized study. Since the evidence which has led to the proposal of structural formulas for the morphine group has been drawn not only from the transformations of morphine, codeine, and thebaine, but also from the behavior of their numerous derivatives, the whole structural evidence is summarized in the concluding chapter.

The nomenclature adopted throughout is that most commonly used in contemporary publications; in case of doubt, the German name has been accepted. This leads to certain unavoidable inconsistencies, as, for example, the universal usage "methylmorphimethine" in contrast to the "des-N-methyl-" (Willstätter, Ann. **317**, 268 (1901))

nomenclature ordinarily applied to methine bases in the German literature. The abbreviations used in the bibliographies are in general those of Chemical Abstracts (see Chem. Abst., List of Periodicals Abstracted, 1926; Chem. Abst. **25**, 6019 (1931)), and, for simplification, in most cases only the first page of the article is cited. Practically all data have been drawn from the original literature; hence Zentralblatt and Chemical Abstracts references are not usually given. Patents have been consulted in the original where possible, and further references made to Friedländer, Fortschritte der Teerfarbenfabrikation; Houben, Fortschritte der Heilstoffchemie; and Wagner's Jahresbericht der Chemischen Technologie. The author has made every attempt to supply copious literature references, and to show the source of every statement made.

The numerous excellent reference books on alkaloid chemistry have been seldom cited in the bibliographies, due to a desire to draw information as far as possible from original sources. A number of these books are here listed for convenience:

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Wolffenstein, Die Pflanzenalkaloide (Springer, Berlin, 1922).

It is a pleasure for the author to acknowledge here his indebtedness to Professor Wieland for his kindness in examining the manuscript, and to Dr. Erich Mosettig, of this laboratory, for many helpful suggestions in the preparation of the text.

LYNDON F. SMALL.

UNIVERSITY, VA., *January 12, 1932.*

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CHEMISTRY OF THE OPIUM ALKALOIDS[a]

Part I. THE BENZYLISOQUINOLINE AND MINORS ALKALOID

PAPAVERINE

Papaverine was discovered in the mother liquors from morphine extraction, by G. Merck (1) (2) (1848), who analyzed the base as well as its hydrochloride and platinichloride, and assigned to it the formula $C_{20}H_{21}O_4N$. Merck's analysis was supported by various other investigators (3) (4) (5) (6).

Deschamps (7) in 1864 isolated a crystalline substance from poppy seed-capsules, which he named papavérin; this seems to have been impure narceine. Another weakly basic substance, "papavérosine," was also described.

In 1870, Hesse (8) (9) (10) obtained from opium a papaverine which analyzed for $C_{21}H_{21}O_4N$. This formula, likewise, found confirmation in other laboratories (11) (12). Indeed, even after the careful researches of Goldschmiedt (13) (14) (15) had shown conclusively that only the formula of Merck came into question for papaverine, Hesse remained by the formula $C_{21}H_{21}O_4N$, as a "Pseudopapaverine," (16) produced by the poppy during the years 1860–1870, (17).[1] Hesse's "pseudopapaverine" was finally eliminated in 1926 by analyses on his original samples (18).

Papaverine is found in all parts of *Papaver somniferum* L. (var. *album*) except the roots, chiefly, however, in the unripe seed-capsules. It is one of the last of the alkaloids to make its appearance in the plant, being first detectable 36 days after the sprouting of the seeds (19). Opium usually contains from 0.5 to 1% of the alkaloid (20) (21) although it may occasionally be totally lacking (e. g., in Bengal opium (22).)

Papaverine is, in general, precipitated along with narcotine in the separation of the alkaloids from opium. Plugge's (23) method consists in treating the mixed hydrochlorides of the opium alkaloids with a concentrated solution of sodium acetate. The precipitate of narcotine and papaverine thus formed is dissolved in the minimum amount of dilute hydrochloric acid, the solution diluted to the point where it contains not more than 0.25% narcotine, and the papaverine precipitated with potassium ferricyanide. Collection of this precipitate after 24 hours and decomposition with dilute sodium hydroxide yields pure papaverine. About 98% of the total amount present separates by this method. Narcotine is obtained from the filtrate from the ferricyanide precipitation by addition of ammonium hydroxide. In the method of Hesse (8) (10) (24), the papaverine is separated from narcotine as the acid oxalate, which crystallizes in a state of great purity (25). Other methods of separation are described by Merck (2), Anderson (3), Kanewskaja (26), and Missenden (27).

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[a] This publication is presented as the result of cooperative work between the Committee on Drug Addiction of the Division of Medical Sciences of the National Research Council and the Division of Mental Hygiene of the United States Public Health Service.

[1] This was not an entirely unreasonable assumption, since the nature and amount of the alkaloids produced by a given plant species may be markedly influenced by climatic and soil conditions.

Pure papaverine crystallizes in rhombic prisms or small white needles, of melting point 147° to 148°. It dissolves in traces in boiling water, is sparingly soluble in ether, readily soluble in hot alcohol, benzene, or glacial acetic acid (13). Solubility: ether 10°, 1:258; benzene 1:36; amyl alcohol 1:77 (28); ethyl alcohol, cold 1:45, hot 1:4; carbon tetrachloride at 17°, 1:495 (29); petroleum ether, cold, sparingly, hot, very soluble.

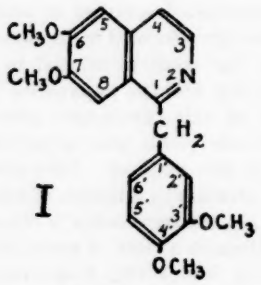
The crystals have the sp. gr. 1.30 to 1.33 (30); N_D, $\alpha = 1.62$, $\beta = 1.68$ (31). The heat of combustion has been determined by Leroy (32) (33), the absorption spectrum by Dobbie and Lauder (34), Steiner (35), Kitasato (36); fluorescence (37). Papaverine is very stable towards heat (38), and sublimes amorphous (31). (*Cf.* Blyth (39).)

Papaverine and its salts are optically inactive (Goldschmiedt (40); *cf.* Hesse (41) Bouchardat and Boudet (42)).

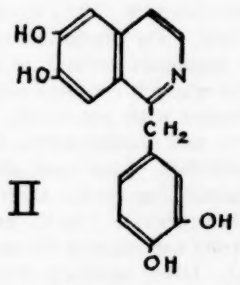
It is a weak mono-acid base, without action on litmus or phenolphthalein (8) (43), but turns methyl orange (32). For titration methods and bibliography of these, see Wales (44).

The numerous qualitative tests which have been described for papaverine are largely worthless, since it has been shown (25) that most of them depend upon the presence of cryptopine in small quantities. With Lafon's reagent (ammonium selenite 1 g., in conc. H_2SO_4, 20 c.c.), a yellow-green, becoming yellow, is obtained. Marquis' reagent (formaldehyde in conc. H_2SO_4) produces a light rose, changing to brown (25). The reaction of papaverine ferricyanide with Marquis' reagent—a light blue color, becoming violet and finally passing through green to dirty yellow—has been proposed as characteristic (45); see also the "Magnol" test of David (46). For estimation of papaverine, see Annett (47). The behavior and limits of sensitivity with a large number of inorganic salts are given by Wagenaar (31) and by Kerbosch (19); silicotungstate (48); lead acetate reaction (49).

The work of Goldschmiedt, extending over a period of 20 years, has shown papaverine to be a tetramethoxy-1-benzyl-isoquinoline, of Formula I:



I Papaverine



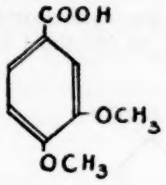
II Papaveroline

It is of particular interest as the first alkaloid in which the presence of the isoquinoline ring was demonstrated.

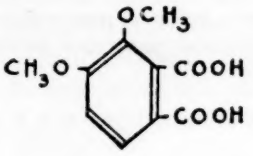
The existence of four methoxyl groups in the molecule is evident from the products obtained by treatment of papaverine with hydriodic acid. Four equivalents of methyl iodide are formed, together with

the phenolic substance papaveroline (Formula II), which is soluble in alkali and easily oxidized by air (50), (51). With fuming hydrochloric acid at 130°, papaverine yields methyl chloride and homopyrocatechol; by dry distillation it is converted to dimethylhomopyrocatechol and methylamine (52).

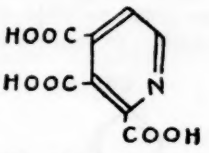
The first evidence concerning the structure of papaverine was gained by oxidation with potassium permanganate in neutral solution, whereby veratric acid, hemipinic acid (supposedly), and 1,2,3-pyridinetricarboxylic acid (α-carbocinchomeronic acid) were formed,



Veratric Acid

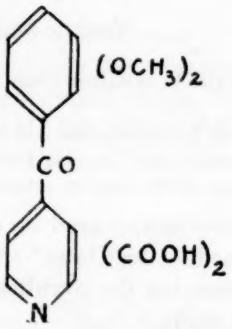


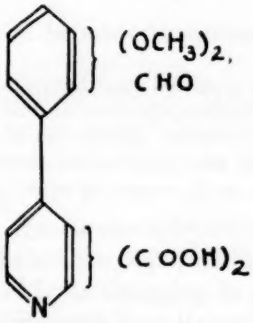
Hemipinic Acid



1,2,3-Pyridinetricarboxylic Acid

together with papaverinic acid:

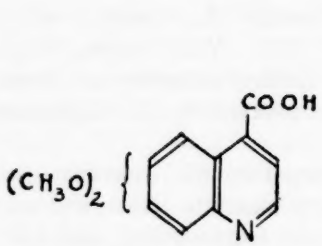




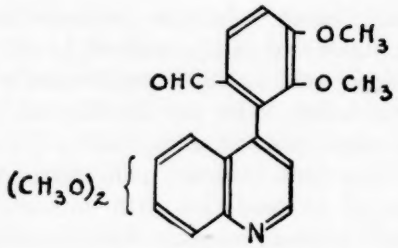
to which was tentatively assigned one of these formulas (53).

The appearance of hemipinic acid among the oxidation products seemed best explained by the assumption of an aldehyde group here, since the seventh oxygen atom of papaverinic acid was definitely shown (52) not to be in a hydroxyl group. Nevertheless, the impossibility of oxidizing this to a carboxyl group seemed remarkable. The ketone formula made it difficult to account for the formation of hemipinic acid.

The permanganate oxidation in acid solution takes a different course, resulting in a new base, papaveraldine, and an acid which was thought to be dimethoxycinchoninic acid (50) (54). Since the latter contains but two methoxyl groups, and the simultaneously formed veratric and hemipinic acids also contain two, the four methoxyl groups of papaverine are equally divided between the nitrogen-containing and nitrogen-free nuclei of the molecule. Since papaveraldine gave the characteristic reactions for a carbonyl group, this seemed to confirm the assumption made in the case of papaverinic acid.



Dimethoxycinchoninic Acid



Papaveraldine (1886)

In general agreement with this, fusion of papaverine with potassium hydroxide was found to yield dimethylhomopyrocatechol (which could be identified by oxidation to veratric acid),

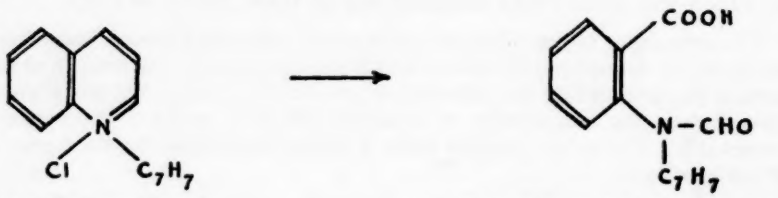
Dimethylhomopyrocatechol

Veratric Acid

and the supposed dimethoxyquinoline, which could also be obtained from heating the "dimethoxycinchoninic acid" (14).

The incorrect assumption of a quinoline nucleus in papaverine led to considerable confusion in the early work of Goldschmiedt, but is considered here because of the reasoning which led to the recognition of the true structure.

The first discrepancies in the quinoline formula appeared on oxidation of the papaverine alkyl halides. According to Claus [2] the oxidation of quinoline alkyl halides results in opening the pyridine ring, with formation of derivatives of anthranilic acid:

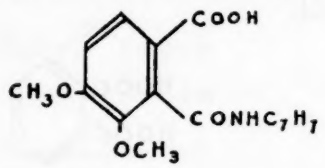


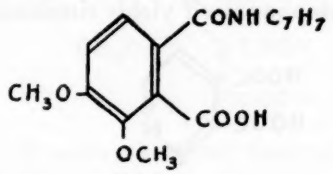
Quinoline Benzochloride

Formyl Benzyl Anthranilic Acid

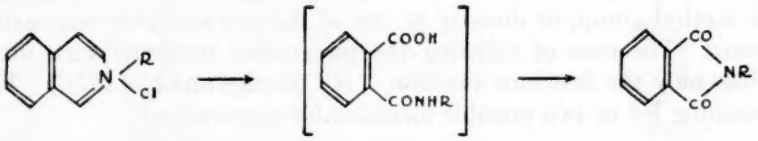
[2] Ber. 16, 1284 (1883).

In contrast to this, oxidation of papaverine benzochloride gave, along with veratric, benzoic, and oxalic acids, and papaveraldine, a benzylhemipinisoimide, the anhydride of one of the two acids:

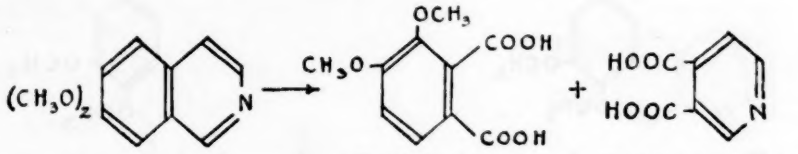




The oxidation of papaverine ethobromide resulted similarly in the formation of an ethylhemipinisoimide which melted at 226°, whereas the hitherto known ethylhemipinimide melted at 98°. Hemipinisoimide was thus shown to be a direct oxidation product of papaverine, which is only possible if the latter is an isoquinoline derivative.



This was confirmed by further evidence: In oxidation of isoquinolines, in part the benzene ring, in part the pyridine ring, is attacked,[3] whereas quinolines on oxidation, give pyridinedicarboxylic acids only. It was, in fact, found that the compound earlier named dimethoxyquinoline oxidized to give hemipinic and cinchomeronic acids (55),



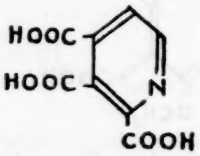
Hemipinic Acid Cinchomeronic Acid

which left but two possible formulas for this dimethoxyisoquinoline:

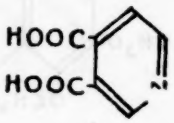
Recognition of the fact that the (supposed) hemipinic acid formed in earlier oxidations was derived from the isoquinoline nucleus made unnecessary the hypothesis of an aldehyde group in the nitrogen-free nucleus of papaverinic acid, and made possible the joining of the two nuclei by a methylene group (56).

[3] Hoogewerff and Van Dorp. Rec. trav. chim. 4, 285 (1885).

The point of attachment of the nitrogen-free portion of papaverine (dimethylhomopyrocatechol) was easily decided (56); oxidation of papaverine gives α-pyridinetricarboxylic acid, whereas dimethoxyisoquinoline itself yields cinchomeronic acid.



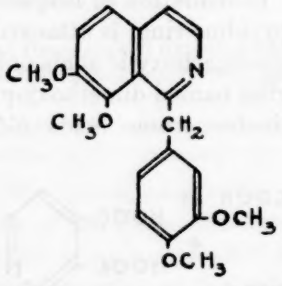
α-Pyridinetricarboxylic Acid

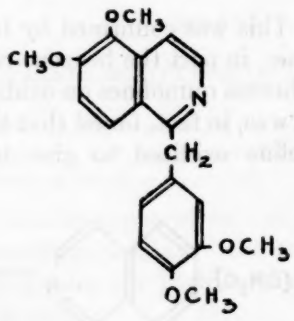


Cinchomeronic Acid

It follows that the other nucleus in papaverine must be linked to that carbon atom corresponding to position 2 in α-pyridinetricarboxylic acid.

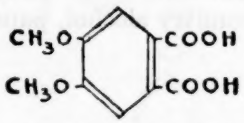
The dimethylhomopyrocatechol group might be attached through the methyl group, or directly to one of the two available ring carbon atoms. The ease of splitting the papaverine molecule with alkali brings only the first into question. (*Cf.* Königs and Nef (57).) This reasoning led to two possible formulas for papaverine:



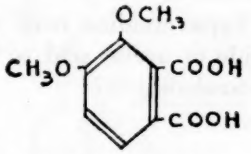


The structure of papaverine was now determined, up to the position of the methoxyl groups in the isoquinoline nucleus. To settle this question, the supposed hemipinic acid obtained through permanganate oxidation was carefully investigated. It showed a remarkable similarity to the known hemipinic acid from narcotine, but differed from this in the melting points of its anhydride and the ethyl imide already mentioned (58). It proved in fact to be an isomer of ordinary hemipinic acid; the carboxyl groups are adjacent (anhydride formation and fluoresceine reaction), and since fusion with potassium hydroxide gives protocatechuic acid, the methoxyl groups are likewise adjacent. This leaves but one possible formula, and the substance was desig-

nated as metahemipinic acid (58) (59) to distinguish it from the hemipinic acid from narcotine. (Proof of structure, p. 64.)

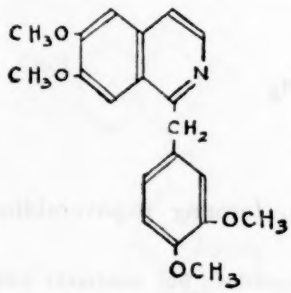


Metahemipinic Acid

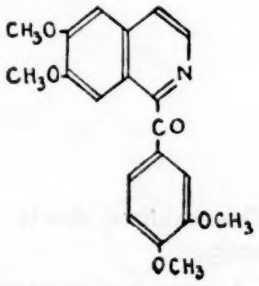


Hemipinic Acid from Narcotine

Papaverine and papaveraldine therefore are to be represented (60) as:

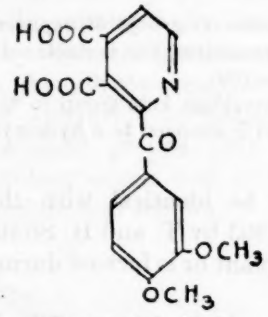


Papaverine

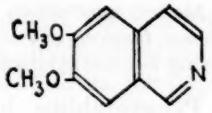


Papaveraldine

and papaverinic acid and the supposed dimethoxyquinoline become:



Papaverinic Acid



Dimethoxyisoquinoline

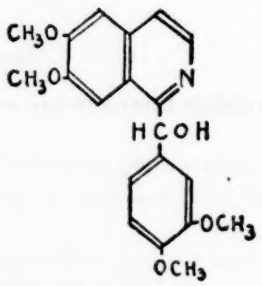
Papaverine was thus the first opium alkaloid whose structure was completely known (1888).

Although papaveraldine has the structure of a tetramethoxybenzoylisoquinoline, the old name was retained to avoid confusion. This structure explains satisfactorily the splitting of papaveraldine by potassium hydroxide into veratric acid and dimethoxyisoquinoline, a reaction parallel to the conversion of benzophenone into benzoic acid and benzene (56) (61) (62).

In accordance with its ketone character, papaveraldine reacts with hydroxylamine and phenylhydrazine (50).

The oxime [4] exists in an α- (labile) form (m. p. 235°) and a β- (stable) form (m. p. 254°). Reduction of the α- form with sodium-amalgam gives papaveraldylamine (64).

Papaveraldine itself may be reduced with zinc and acetic anhydride or acetic acid to papaverine [5] or to a secondary alcohol, papaverinol (66) (67).



Papaverinol

This oxidizes slowly in alkaline solution, forming papaveraldine again.

Acetylation of papaverinol has not been accomplished, but treatment with p-bromobenzoyl chloride gave a benzoyl derivative, and phenylisocyanate yielded a phenylurethane (66).

Oxidation of papaverine in dilute acetic acid with mercuric acetate gives a quantitative yield of papaverinol (68).

By the action of aluminum chloride, the four methoxyl groups of papaveraldine are converted to hydroxyls, resulting in papaveraldoline; this is stable only in the form of its salts or the pentabenzoyl derivative (69).

Methyl magnesium iodide reacts with the papaveraldine keto group in the normal fashion, but at the same time the 7-methoxyl is changed to a hydroxyl, giving 7-demethylomethylpapaverinol (70).

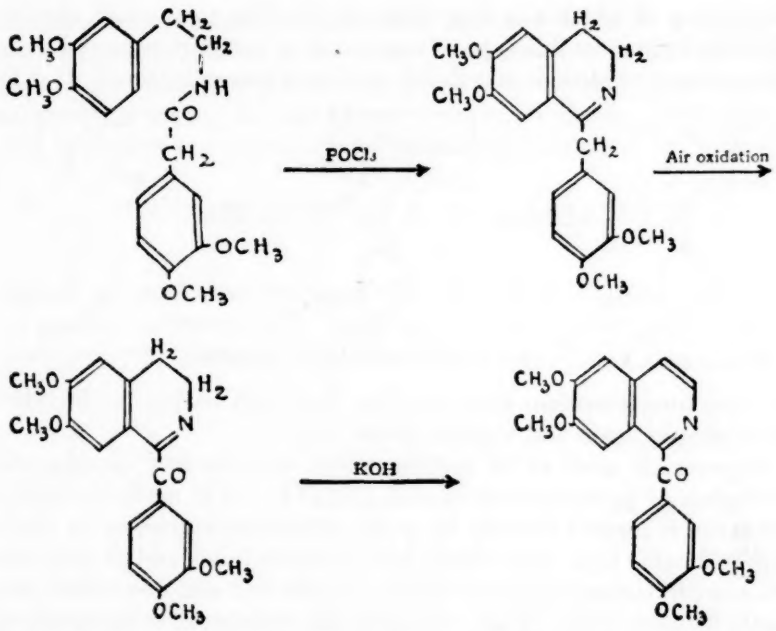
Papaveraldine has been shown (61) to be identical with the alkaloid xanthaline obtained from opium in 1893 by T. and H. Smith (71); whether it occurs as such in the poppy plant or is formed during the extraction operations is not known.

The synthesis of papaveraldine (which is equivalent to a synthesis of papaverine) has been accomplished (67) through condensation of homoveratroyl-homoveratrylamine and oxidation of the product:

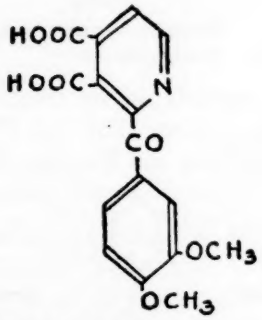
---

[4] Papaveraldoxime results likewise from the action of sodium nitrite on papaverine hydrochloride (63).

[5] Buck, Perkin, jr., and Stevens (65) were unable to reproduce this, but found that papaverinol could be converted to papaverine by the action of an acetic acid solution of hydrogen bromide, followed by reduction with zinc dust.



Papaverinic acid is a dibasic acid produced by moderately vigorous oxidation of papaverine. Papaverinol and papaveraldine undoubtedly represent the intermediate stages of this oxidation process. It contains a ketonic carbonyl group (forming readily an oxime and a phenylhydrazone), and two methoxyl groups (50) (72). The ease of anhydride formation indicates the ortho-position for the two carboxyl groups (73). Fusion with potassium hydroxide yields protocatechuic acid (53). From these facts, the formula for papaverinic acid follows:

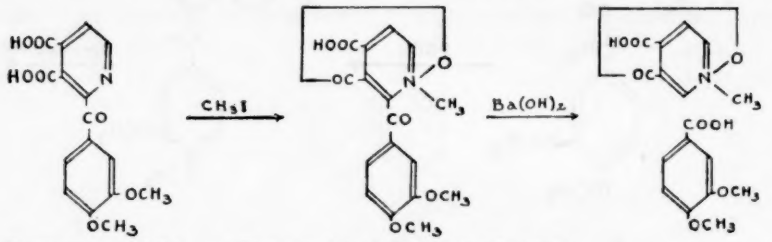


Papaverinic Acid (α-Veratroyl Cinchomeronic Acid)

Papaverinic acid yields two distinct monomethyl esters, and a dimethyl ester (74) (75) (76) (77) (78).

Vigorous treatment of papaverinic acid with methyl iodide results in the formation of papaverinic acid methylbetaine (79) (80), the

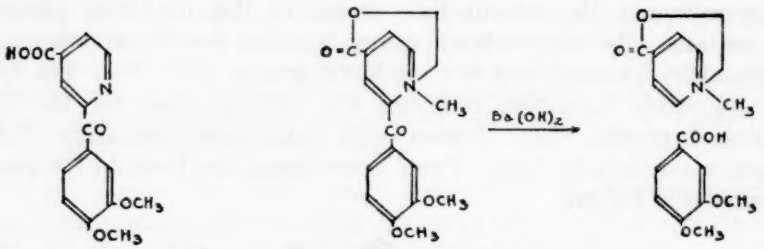
recognition of which was long delayed (74), due to the fact that the N-methyl group in this type of compound is partially removed under the ordinary conditions of a Zeisel methoxyl determination (75) (81).[6]



Papaverinic Acid Papaverinic Acid Methylbetaine

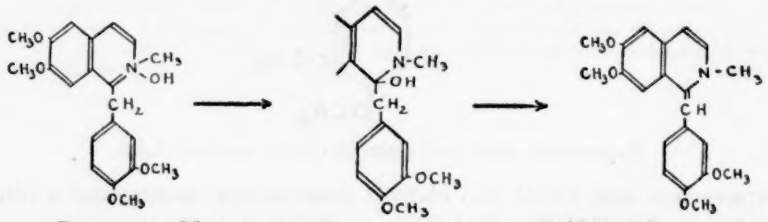
Its structure is evident from the fact that with barium hydroxide it gives apophyllenic and veratric acids (75).

Papaverinic acid, at its melting point, loses carbon dioxide, with formation of pyropapaverinic acid (53) (72). The methylbetaine of the latter is formed directly by action of methyl iodide, or by loss of carbon dioxide from papaverinic acid methylbetaine, and on decomposition with barium hydroxide gives veratric acid and isonicotinic acid methylbetaine (75). This confirmed the structure for pyropapaverinic acid which had already been deduced from the behavior of the isomeric papaverinic acid monomethyl esters on heating (74).



Pyropapaverinic Acid (Veratroylisonicotinic Acid) Pyropapaverinic Acid Methylbetaine

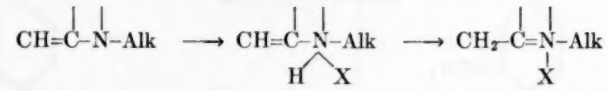
The alkyl halides of papaverine, on treatment with concentrated alkali, give alkyl isopapaverines (82), (*cf.* Claus and Hüetlin (12), Claus and Edinger (83), Claus and Kassner (84) (85))



Papaverine Methohydroxide N-Methyl Isopapaverine

[6] Bush. Ber. **35**, 1515 (1902). Goldschmiedt and Hönigschmid. Monatsh. **24**, 707 (1903).

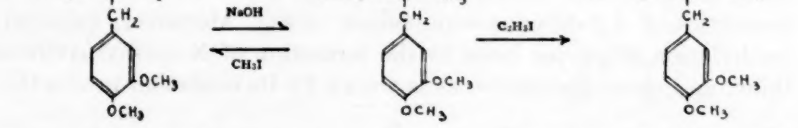
a general reaction of cyclammonium bases holding a primary or secondary alkyl group in the α- or γ- positions (86). The alkyl isopapaverine bases are colored, but dissolve in water to form colorless alkaline solutions of the alkyl papaverinium hydroxide. With halogen acid they give the normal papaverine alkyl halide:



The structure of these isopapaverines is evident from the products of potassium permanganate oxidation, veratric acid, and N-alkyl-dimethoxyisoquinolones (87) (88) (89).

N-Alkyl Isopapaverine Veratric Acid

The action of dilute alkali on papaverine alkyl halides results in N-alkyl phenolbetaines (90)[7], from papaverine methiodide for example, N-methylnorpapaverinium betaine. Vigorous action of methyl iodide on this regenerates papaverine methiodide. By the action of ethyl iodide, the methiodide of the new homopapaverine is obtained.*



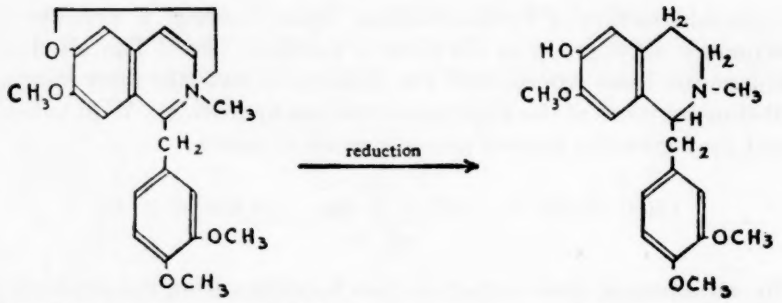
Papaverine Methiodide Homopapaverine Methiodide

N-Methylnorpapaverinium Betaine

Nitration of homopapaverine methiodide and splitting of the molecule by the method of Pschorr (93) gives nitrohomoveratrol, showing that the ethoxyl group is in the isoquinoline ring. Reduction of N-methylnorpapaverinium betaine results in pseudolaudanine (94); determination of the structure of the latter (95) has shown that the betaine oxygen of the norpapaverinium compounds must be linked in the 6-position.

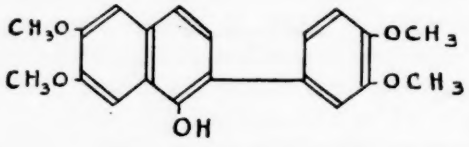
[7] Goldschmiedt and Stransky mistook these for papaverinium alkyl hydroxides (91) (92).

* See Appendix, p. 357.

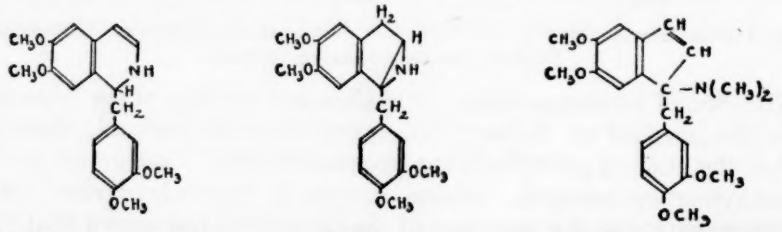


N-methylnorpapaverinium Betaine — Pseudolaudanine

Alcoholic potassium hydroxide causes a deep-seated change in papaverine alkyl halides, whereby a nitrogen-free naphthol derivative is formed, probably through a complicated rearrangement involving the carbinol form of the alkyl papaverinium hydroxide (96).



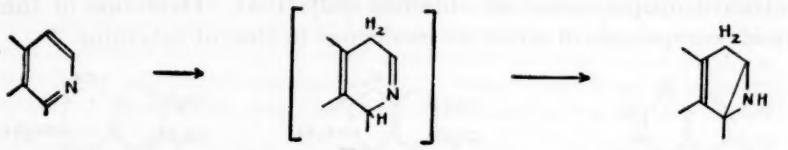
Several reduction products of papaverine are known. By the action of tin and hydrochloric acid, a dihydropapaverine is formed (pavine) (97) (98) (99), a crystalline substance of m. p. 200° to 201°, which Goldschmiedt (54) (100), who first prepared it, believed was tetrahydropapaverine. In contrast to papaverine, pavine may be resolved into optically active components (101),[8] showing that an asymmetric carbon atom has been generated by the reduction. The formation of a nitrosamine (100) shows the presence of an imino group, therefore the added hydrogen was supposed to have gone in the 1,2-position. Pavine is, however, very resistant to oxidation (103) or to further reduction (99), which is not in accord with the properties of 1,2-dihydroisoquinolines (104). Moreover, exhaustive methylation of pavine leads to the formation of N-methylpavinemethine, an indene derivative, as is shown by its oxidation products.



1,2-Dihydropapaverine — Pavine — N-Methylpavinemethine

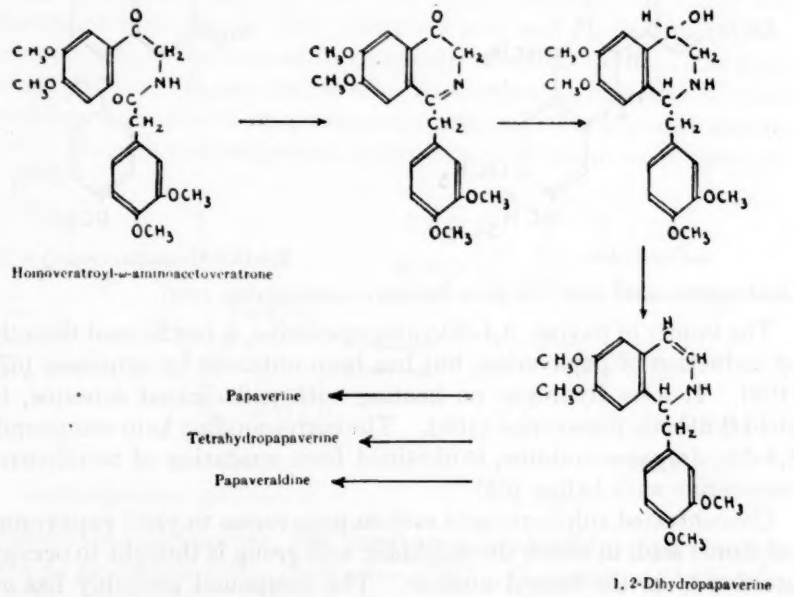
[8] In connection with this resolution, Pope and Peachy (102) found that the α-halogenocamphorsulphonic acids were far better adapted than tartaric acid, since the latter, being dibasic, led to the formation of "hemiracemic" compounds, consisting of one molecule of *d*-tartaric acid in combination with one *d*- and one *l*-molecule of the base. Goldschmiedt (100) was unable to accomplish the resolution, using tartaric acid.

The properties of pavine are therefore best explained by a formula containing a bridge bond between the 1,3-carbon atoms. Addition of hydrogen to papaverine has probably taken place in the 1,4-positions, with subsequent rearrangement (98):



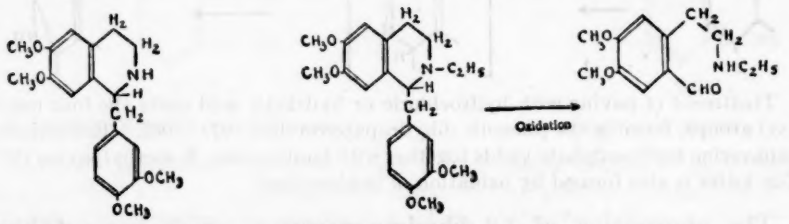
Treatment of pavine with hydrochloric or hydriodic acid splits the four methoxyl groups, forming the phenolic dihydropapaveroline (97) (100). Reduction of papaverine methosulphate yields together with laudanosine, N-methylpavine (99). The latter is also formed by oxidation of laudanosine.

The preparation of 1,2-dihydropapaverine, which has not been possible starting from papaverine, has been accomplished by synthesis (143). The starting point for this was homoveratroyl-ω-aminoacetoveratrone; the steps involved are shown on the diagram below. The proof of structure given included conversion to tetrahydropapaverine by catalytic reduction, to papaverine by dehydrogenation, and to papaveraldine by oxidation, which constitutes new syntheses of these substances.



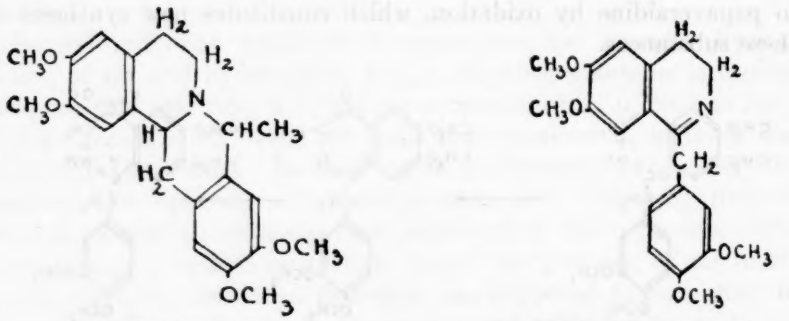
The chief product of the reduction of papaverine with tin and hydrochloric acid is an amorphous substance, tetrahydropapaverine, which may be isolated as the crystalline hydriodide (97). Tetrahydropapaverine is likewise formed by electrolytic reduction of

papaveraldine (105) or papaverine (106). The reversal of this reaction, conversion of tetrahydropapaverine to papaverine was accomplished by heating the former with palladinized asbestos (106). By reduction of papaverine alkyl halides, the corresponding N-alkyl tetrahydropapaverines are obtained (93) (103). Oxidation of these yields compounds of structure analogous to that of cotarnine. *



Tetrahydropapaverine N-Ethyltetrahydropapaverine

With acetal, tetrahydropapaverine condenses to form α- and β-coralydine (107), a reaction analogous to the Pictet and Gams [9] tetrahydroberberine synthesis. α-Coralydine, which has the following structure, differs from the natural alkaloid corydaline only in the position of the methoxyl groups in the veratryl nucleus:



α-Coralydine 3,4-Dihydropapaverine

Condensation with methylal gives similarly norcoralydine (108).

The isomer of pavine, 3,4-dihydropapaverine, is not formed directly by reduction of papaverine, but has been obtained by synthesis (67) (109). It loses hydrogen on heating with palladinized asbestos, to yield synthetic papaverine (106). The corresponding keto compound, 3,4-dihydropapaveraldine, is obtained from oxidation of tetrahydropapaverine with iodine (65).

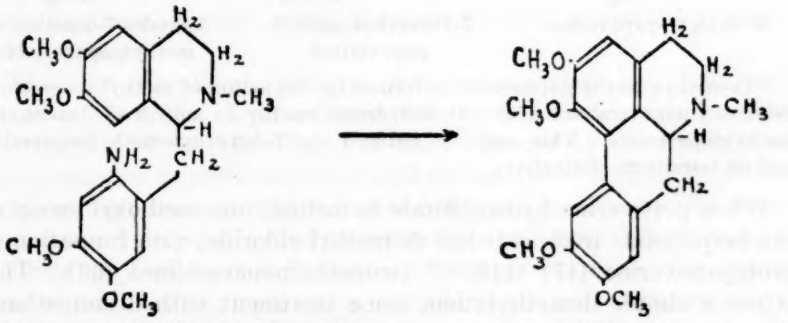
Concentrated sulphuric acid acts on papaverine to yield papaverine sulphonic acid, in which the sulphonic acid group is thought to occupy position 6′ in the benzyl nucleus. The compound probably has an inner salt structure. (145) (*Cf.* Zahn, Biochem. Zeit. **68**, 467 (1915)).

[9] Pictet and Gams. Ber. 44, 2480 (1911).

* See Appendix, p. 357.

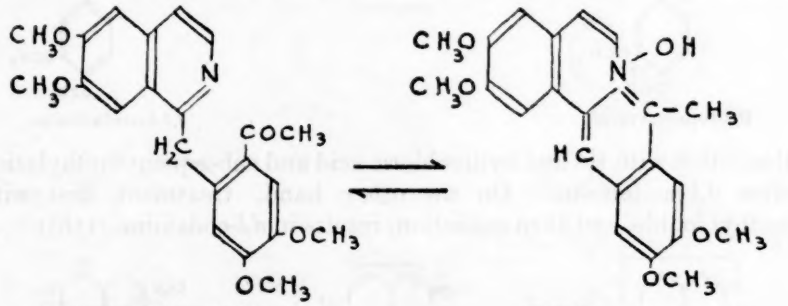
Papaverine reacts with bromine to form a monobromo derivative (3) (13) in which the bromine occupies the 6′-position in the veratryl ring, since oxidation of the corresponding isopapaverine bases leads to formation of 6-bromoveratric acid (87).

Nitropapaverine (3) (9) (10) likewise has the nitro group in the 6′-position (93) (110). Reduction of nitropapaverine methochloride yields an amino-tetrahydro-N-methylpapaverine (*d*, *l*-aminolaudanosine), whose diazonium compound undergoes with copper powder a phenanthrene ring closure to phenanthreno-N-methyltetrahydropapaverine (93).[10] This substance has an interesting similarity to apomorphine, and Gadamer (111) has shown it to be identical with *d*, *l*-glaucine.



Amino-tetrahydro-N-methylpapaverine — *d*, *l*-Glaucine

Papaverine undergoes another interesting condensation under the influence of sulphoacetic acid (sulphuric acid and acetic anhydride), to compounds of the type of the corydalis alkaloids (112). The first product obtained is acetopapaverine (ψ-coralyn), which is a neutral pseudobase, but which in aqueous-alcoholic solution becomes slowly alkaline through rearrangement to the true ammonium base, coralyn:



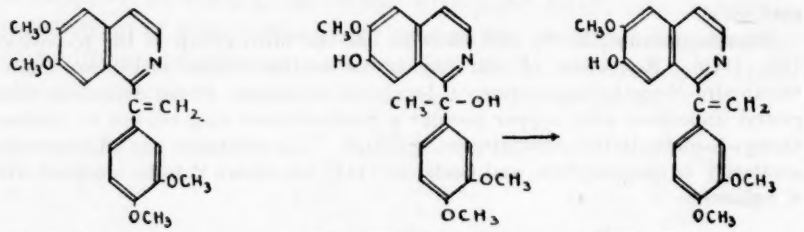
Acetopapaverine (ψ-Coralyn) — Coralyn

Pseudocoralyn methiodide, like papaverine methiodide, may be converted to an isopapaverine derivative (113) (114) (method of Decker and Klauser (82)).

Heating papaverine in a sealed tube with formaldehyde causes condensation on the methylene carbon atom, giving methylene-

[10] According to Gadamer (111), the substance which Pschorr obtained was actually *d*, *l*-laudanosine methiodide, but the desired phenanthreno compound may be isolated from the reaction mixture.

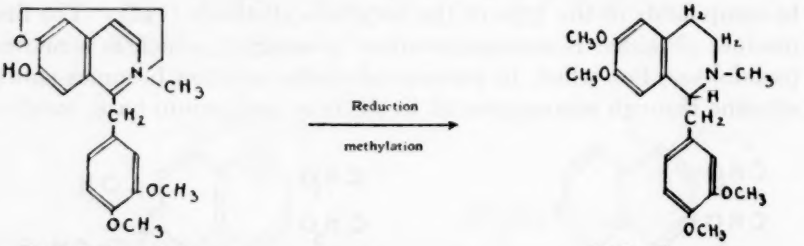
papaverine (115). This may be reduced by hydrogen in the presence of palladium to dihydromethylene-papaverine (18).



Methylene-papaverine | 7-Demethylomethyl-papaverinol | Anhydro-7-demethylo-methylpapaverinol

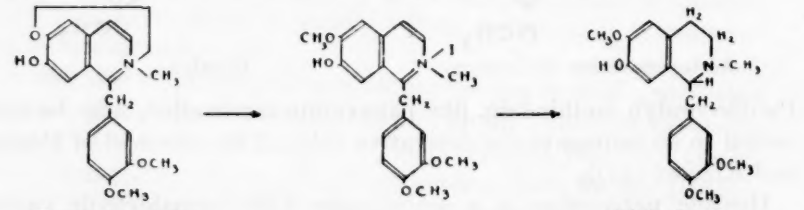
7-Demethylomethylpapaverinol is formed by the action of methyl magnesium iodide on papaveraldine (70). It dehydrates readily to anhydro-7-demethylomethylpapaverinol. This may be reduced to 7-demethylomethylpapaverine and its tetrahydro derivative.

When papaverine hydrochloride is melted, one methoxyl group of the isoquinoline nucleus is lost as methyl chloride, with formation of protopapaverine (17) (116)[11] [12] (trimethylpapaveroline) (63). This is not a simple demethylation, since treatment with diazomethane does not give papaverine again. Analysis shows two methoxyl groups, and a methylimido group. The conversion of protopapaverine to known opium alkaloids indicates clearly its structure (116):



Protopapaverine | *d,l*-Laudanosine

Reduction with tin and hydrochloric acid and subsequent methylation gives *d,l*-laudanosine. On the other hand, treatment first with methyl iodide, and then reduction, results in *d,l*-codamine (116):



Protopapaverine | *d,l*-Codamine

[11] The term "protopapaverine" has also been used to designate the parent substance of papaverine, 1-benzylisoquinoline (65).

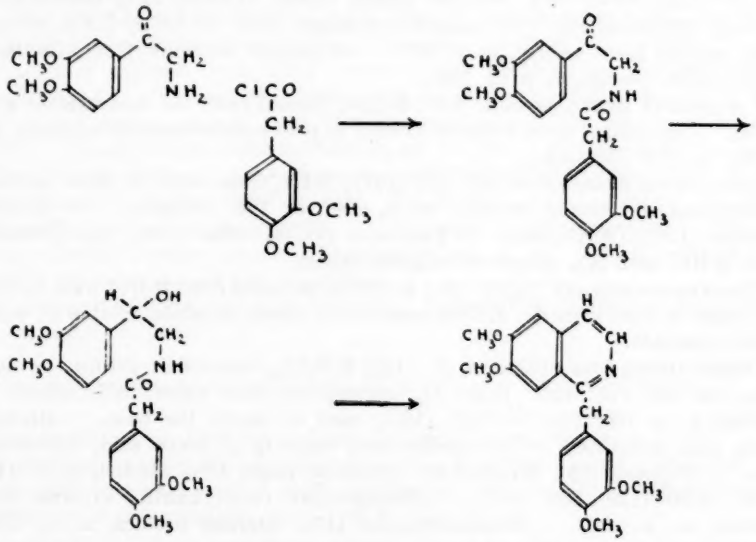
[12] At the same time lesser amounts of N-methylnorpapaverinium betaine hydrochloride, and the isomeric compound with the betaine linkage to oxygen in the 7-position, are obtained.

Methylation of protopapaverine with diazomethane results in the formation of the N-methylnorpapaverinium betaine of Decker, the structure of which has already been discussed.

The ana- (5-) hydrogen atom of papaverine is particularly active, as is the case with narcotine. Condensation takes place at this point with opianic acid or formaldehyde in the presence of sulphuric acid, with formation of opianylpapaverine and methylene-di-papaverine respectively (117).

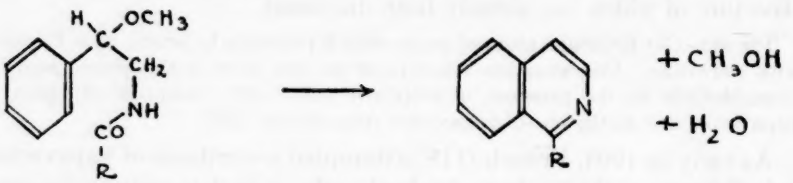
As early as 1903, Fritsch (118) attempted a synthesis of papaverine (*cf.* Pomeranz (142)) but obtained only a higher-melting isomer. Pictet and Finkelstein (109) were able to carry a synthesis as far as 3, 4-dihydropapaverine, which has recently been converted to papaverine (106).

The first completed synthesis was accomplished by Pictet and Gams (119) (120). Veratrol and homoveratric acid served as the starting points for this. Veratrol was converted by the Friedel and Crafts reaction to acetoveratrone, and the isonitroso derivative of this, reduced with tin and hydrochloric acid gave aminoacetoveratrone. Aminoacetoveratrone hydrochloride condensed with homoveratroyl chloride to yield homoveratroyl-ω-aminoacetoveratrone. By reduction of one carbonyl group, a secondary alcohol, homoveratroylhydroxyhomoveratrylamine, was formed, which now under the influence of phosphorous pentoxide underwent the typical isoquinoline ring closure with loss of two molecules of water.



Other syntheses have been carried out by Buck, Haworth and Perkin, jr. (67) (synthesis of papaveraldine), by Rosenmund, Notnagel, and Riesenfeldt (121), and by Mannich and Walther (122).

The methods of Rosenmund and of Mannich depend upon the following isoquinoline synthesis:



The synthesis of papaverine and papaveraldine through 1,2-dihydropapaverine, carried out by Buck (143), has already been described. An attempted Rügheimer synthesis by Allen and Buck (144) was unsuccessful.*

Descriptive Part (Papaverine)

Papaverine Salts (B=$C_{20}H_{21}O_4N$)

Papaverine hydrochloride (1) (2) (10): B·HCl, from water or alcohol, monoclinic crystals (13) (123) (124), m. p. 220° to 221° (225° to 226° (18)), with decomp. to protopapaverine (17) (116). Soluble in 37.3 parts of water at 18° (10). Thermochemistry, Leroy (32). —Platinichloride (1) (2) (8) (13), $(B{\cdot}HCl)_2PtCl_4+2H_2O$, orange, rhombic microcrystals from boiling HCl, m. p. 198° (196° (119) 212° to 213° (18)),+ ½ H_2O, m. p. 186° (21). —Mercurichloride (8) (13), $(B{\cdot}HCl)_2\ HgCl_2$, rhombic leaflets or triclinic prisms. —Zinc chloride (13), $(B{\cdot}HCl)_2\ ZnCl_2$, right-angled leaflets, decomp. on drying (*cf.* Mayer (125), Hesse (9)). —Zinc iodide (126), $(B{\cdot}HCl)_2\ ZnI_2$, leaflets from alcohol, light-sensitive. —Cadmium chloride (126), $(B{\cdot}HCl)_2\ CdCl_2$, tetragonal crystals from alcohol, m. p. 176°. —Cadmium bromide (126), $(B{\cdot}HCl)_2\ CdBr_2$, white precip., m. p. ca. 185°.

Papaverine hydrobromide (13): B·HBr, formed from the acid oxalate with $CaBr_2$. Crystallizes from water or alcohol in pale yellow monoclinic prisms, m. p. 213° to 214° (decomp.).

Papaverine hydriodide (13) (17) (127): B·HI, from water or dilute alcohol, dimorphous monoclinic crystals, m. p. 200° or 196° (decomp.). —Mercuriodide (126), $(B{\cdot}HI)_2HgI_2$. —Triiodide (3) (4) (126) (128), $B{\cdot}HI_3$, formed from B·HCl with KI_3, purple rectangular prisms.

Papaverine nitrate (2) (8) (13): $B{\cdot}HNO_3$, prepared from B·HCl with $AgNO_3$, or excess of base with dil. HNO_3; monoclinic, glassy crystals, soluble in warm water, unstable.

Other salts: Acid sulphate (1) (13): $B{\cdot}H_2SO_4$, monoclinic prisms. —Acid oxalate (10) (13) (25), $B{\cdot}H_2C_2O_4$, crystallizes from water, diff. soluble in alcohol, m. p. 196° (201° to 202° (18)); used to purify the base. —Bichromate (13), $B{\cdot}H_2Cr_2O_7$, yellow needles from water or gl. acetic acid; light-sensitive. —Picrate (13), $B{\cdot}C_6H_3N_3O_7$, quadratic plates from alcohol, m. p. 179° (183° (119) (129) 186° (18)). —Picronolate (119), hairlike crystals from alcohol, m. p. 220°. —Sulphocyanate (17), colorless needles, m. p. 152°, soluble in hot but not in cold water, useful to purify papaverine. —Succinate (126), $B_2{\cdot}C_4H_6O_4$, plates from alcohol, soluble in hot water, m. p. 171°. —Benzoate (126), $B{\cdot}C_7H_6O_2$, triclinic crystals from alcohol, insoluble in water, m. p. 145°. —Salicylate (126), $B{\cdot}C_7H_6O_3$, monoclinic, m. p. 130°.*

* See Appendix, p. 357.

PAPAVERINE METHIODIDE (12) (13) (83) (90) (91) (130): $B{\cdot}CH_3I+4H_2O$, from components in sealed tube at 100°, 20 hours. Nearly white leaflets from dilute alcohol, m. p. 60° to 65°, anhydrous 195° (*cf.* p. 675, note 3 of ref. 92). —METHOMETHYLSULPHATE (88) (90), $B{\cdot}(CH_3)\ (SO_4CH_3)$, hygroscopic crystals. —METHOSULPHATE (84), hygroscopic, m. about 110°.

PAPAVERINE ETHIODIDE (12) (90): $B{\cdot}C_2H_5I$, granular yellow crystals from water or alcohol, m. p. 216° decomp. —ETHOBROMIDE (90), $B{\cdot}C_2H_5Br+4H_2O$, from base with C_2H_5Br, sealed tube 10 hours at 100°. Light yellow crystals from water. Anhydrous, m. p. 206° to 207°. (*Cf.* Claus (12), Goldschmiedt (13).) Confused by Goldschmiedt (92) with norpapaverine ethobromide. Crystal measurements, Claus (140). —ETHOCHLORIDE (12) (126), $B{\cdot}C_2H_5Cl+4H_2O$, efflorescent prisms: Platinichloride (12) (92), $(B{\cdot}C_2H_5Cl)_2PtCl_4$, m. p. ca. 223°, decomp. —ETHONITRATE (12), $B{\cdot}C_2H_5NO_3+3H_2O$, faintly green prisms. —ETHODICHROMATE (84) (91), $(B{\cdot}C_2H_5)_2\ Cr_2O_7$, m. p. 139°.

PAPAVERINE ISOPROPIODIDE (87): From alcohol, m. p. 93° to 94°. —PROPOSULPHATE, $(+2H_2O)$, m. p. 126°. —PROPOCHLORIDE, m. p. 80°. —PROPOHYDROXIDE, needles or leaflets (84). (*Cf.* Decker and Dunant, note 38 of ref. 90.)

PAPAVERINE BUTOBROMIDE (87): $B{\cdot}C_4H_7Br+2H_2O$, m. p. 109°, anhydrous 217° (decomp.). —BUTOCHLORIDE (87), $B{\cdot}C_4H_7Cl+2H_2O$, m. p. 131° to 132°; -Mercurichloride, decomp. 200°; -Platinichloride, m. p. 204°. —BUTOPICRATE (87), (from butylisopapaverine and picric acid), m. p. 151° to 152°. —ISOBUTIODIDE (87), yellow prisms from alcohol, m. p. 171° to 172°.

PAPAVERINE AMYLIODIDE (126) and AMYLBROMIDE are noncrystalline.

PAPAVERINE CYANOMETHOBROMIDE (131): $B{\cdot}(CH_2CN)Br$, from the action of bromacetonitrile; crystalline powder from alcohol, m. p. 204°.

PAPAVERINE BENZOCHLORIDE (55) (91): $B{\cdot}C_7H_7Cl+7(9?)H_2O$, no definite m. p. (13), octahedral (12). (*Cf.* Decker and Dunant (90)): Platinichloride (12) (13), $(B{\cdot}C_7H_7Cl)_2PtCl_4$. —BENZODICHROMATE (84) (91), microscopic crystals, decomp. on heating. —o-NITROBENZO (132); -Chloride, $B{\cdot}C_7H_6NO_2Cl+$variable H_2O. Light yellow crystals from water, decomp. 140° to 150°; forms a crystalline platinichloride: -Nitrate, $B{\cdot}C_7H_6NO_2{\cdot}NO_3+1\frac{1}{2}H_2O$; -Picrate, m. p. 215°; Dichromate, yellow prisms. —p-NITROBENZOCHLORIDE (87), yellow crystalline powder, decomp. 132°; -Mercurichloride, m. p. 188°; -Picrate, 183° to 184°.

PAPAVERINE PHENACYL: — BROMIDE (133), $B{\cdot}C_6H_5COCH_2Br+1\frac{1}{2}$ or $2H_2O$, yellow pyramids, decomp. 190° to 194°. —NITRATE, yellow needles m. p. 173° (decomp.). —PICRATE, m. p. 182°. —DICHROMATE, yellow needles. —CHLORIDE, $(+6H_2O)$ yellow needles, hygroscopic, m. p. ca. 114°. —SULPHATE and PLATINICHLORIDE are also crystalline.

PAPAVERINE o-XYLYLENE BROMIDE (134): $B_2{\cdot}C_6H_4(CH_2Br)_2$ needles from alcohol, m. p. 207° to 208°.

PAPAVERINE ETHOXYPROPYLATE: $C_{20}H_{21}O_4{\equiv}N\begin{matrix}OC_2H_5\\C_3H_7\end{matrix}$ colorless needles m. p. 137° (84) (85). (*Cf.* Decker and Dunant, note 38 of ref. 90.)

N-METHYLPAPAVERINE-p-TOLUENESULPHONATE: From papaverine and p-toluenesulphonic acid methyl ester, sealed tube; m. p. 171°. N-ALLYLPAPAVERINEBENZENESULPHONATE, m. p. 174° to 175° (141).

PAPAVERINE DERIVATIVES

PAPAVERALDINE: $B{=}C_{20}H_{19}O_5N$. Formed by treatment of papaverine, dissolved in sufficient dilute sulphuric acid to form the acid salt, with cold 2% potassium permanganate solution, as long as the latter decolorizes. The MnO_2 precip., on extraction with alcohol, gives a 50% yield of pure papaveraldine, a

yellow crystalline powder, m. p. 210°, insol. in water, alkali or carbonates, soluble in hot gl. acetic acid or conc. mineral acids. Slightly sol. in ether, alcohol, petroleum ether, soluble in benzene or chloroform (50) (54) (69) (93). —HYDROCHLORIDE, $B{\cdot}HCl+2\frac{1}{2}H_2O$, yellow crystals; from alcohol anhydrous. —ACID SULPHATE, $B{\cdot}H_2SO_4$ yellow needles, decomp. by water. —PLATINICHLORIDE, $(B{\cdot}HCl)_2PtCl_4+H_2O$, orange-red prisms, decomp. ca. 220°. —PHENYLHYDRAZONE, doubtfully crystalline, m. p. ca. 80° to 85° (50). —NITRATE, $B{\cdot}HNO_3+2H_2O$, yellow needles, decomp. by boiling water. —PICRATE, yellow needles, m. p. 208° to 209°. —METHIODIDE, $B{\cdot}CH_3I+2H_2O$ (from sealed tube at 100°), yellow prisms, m. p. 135° (decomp.). —ETHOBROMIDE $B{\cdot}C_2H_5Br+3H_2O$ (from sealed tube, 145°), prisms or needles, melting above 270° with blackening (54). —METHOMETHYLSULPHATE (62) $B{\cdot}(CH_3)_2SO_4+CH_3OH$, yellow microcrystalline powder. —OXIME, (63) (64), $C_{20}H_{20}O_5N_2$, α (labile) form m. p. 235°; β (stable) form m. p. 254°: Oxime Hydrochlorides, $C_{20}H_{20}O_5N_2{\cdot}2HCl$: $(+12H_2O)$ m. p. 80° to 86°, anhydrous ca. 195°; $(+4H_2O)$ m. p. 95°, anhydrous, m. p. 170°; $C_{20}H_{20}O_5N_2{\cdot}HCl$: $(+3H_2O)$ yellow needles; $(+10H_2O)$ white rhombic prisms, sinters at 90°, decomp. 220° to 225°, anhydrous, m. p. 185° to 187°. PAPAVERALDYLAMINE, $C_{20}H_{22}O_4N_2$, from reduction of the α-oxime, m. p. 80° to 85° (64). NITROPAPAVERALDINE (93), $C_{20}H_{18}O_7N_2$, from oxidation of nitropapaverine, or nitration of papaveraldine. Hairlike yellow crystals from alcohol or acetic acid, m. p. 199° to 200°. AMINOPAPAVERALDINE, $C_{20}H_{20}O_5N_2$, from reduction of nitropapaverine, m. p. 171° to 172°, diazoniumsulphate m. p. 225°. ANTHRANILOPAPAVERINE, from partial reduction of nitropapaveraldine, m. p. 244° to 245° (93).

3,4-DIHYDROPAPAVERALDINE: (67), $C_{20}H_{21}O_5N$. Synthetic. m. p. 190° to 191°. —HYDROCHLORIDE, dec. 183°. —HYDRIODIDE, m. p. 186°. —OXIME, m. p. 247° to 248°. Oxidation of the base gives papaveraldine. See also Buck, Perkin, jr. and Stevens (65).

PAPAVERALDOLINE: $C_{16}H_7ON(OH)_4$ from action of $AlCl_3$ on papaveraldine. —SULPHATE, decomp. over 200°. —PENTABENZOYL derivative, m. p. 209° (69).

PAPAVERINOL (66) (67): $B=C_{20}H_{21}O_5N$; from reduction of papaveraldine in hot gl. acetic acid with zinc dust, or in quantitative yield by oxidation of papaverine with mercuric acetate (68). White monoclinic needles from methyl alcohol, m. p. 137°, very soluble except in water or ether. May be reduced to papaverine by hydrogen bromide in gl. acetic acid, followed by treatment with zinc dust (65). — HYDROCHLORIDE (66), $B{\cdot}HCl$, precip. oily, becomes crystalline, yellow united needles, m. p. 200° to 202° (decomp.). —PLATINICHLORIDE, $(B{\cdot}HCl)_2PtCl_4$, dec. 168°. —PICRATE, green-yellow prisms from alcohol, m. p. 168° to 171°. —METHIODIDE, $B{\cdot}CH_3I$, decomp. 190°, 200°. —METHOCHLORIDE, white needles, m. p. 178° to 182° (decomp.). —ETHOBROMIDE, $B{\cdot}C_2H_5Br$, yellow prisms, decomp. 167° to 172°. —BENZOCHLORIDE, $B{\cdot}C_7H_7Cl$, m. p. 170° to 178°. —p-BROMOBENZOYL derivative, m. p. 190°. —PHENYLURETHANE, m. p. 180°.

PAPAVEROLINE (50) (51): $C_{16}H_{13}O_4N+2H_2O$, prepared by the action of conc. hydriodic acid and red phosphorous on papaverine; in 90% yield from papaverine with $AlCl_3$ (69) decomp. about 260°. —HYDROCHLORIDE, $(+2H_2O)$ white needles. —NEUTRAL SULPHATE, $(+8\frac{1}{2}H_2O$ or $10H_2O)$ crystals sparingly soluble in water. —OXALATE, $(+3H_2O)$ grouped needles, soluble in hot water (51). —METHIODIDE, m. p. 77°. —METHOCHLORIDE, from papaverine methochloride at 160° with conc. HCl, m. p. 235°. —ETHOCHLORIDE, m. p. 215°. —PROPOBROMIDE, m. p. 140°. —BENZOCHLORIDE, m. p. 158° (84) (85). N-METHYLPAPAVEROLINE, colorless crystals, m. p. 232° (from N-Methylnorpapaverinium betaine) (90). BROMOPAPAVEROLINE PICRATE, dec. 241° (69).

DIMETHYLPAPAVEROLINE (63): Amorphous; –Picrate, m. p. 104°. TRIMETHYLPAPAVEROLINE (63), see protopapaverine.

PAPAVERINIC ACID (53), (72): $C_{16}H_{13}O_7N+H_2O$, from oxidation of papaverine in water suspension with potassium permanganate, separated from veratric acid by crystallization from alcohol. Crystallizes from dilute alcohol, gl. acetic acid, amyl alcohol or very dilute hydrochloric acid. M. p. 233°, violent gas evolution. Dibasic, decomposes carbonates, forms normal and acid salts. The Ba, Ca, Cu, Ag, and K salts are described (53). —HYDROCHLORIDE, $C_{16}H_{13}O_7N\cdot HCl$, orange-red granules; $+2\frac{1}{2}H_2O$, yellow needles.

PAPAVERINIC ACID β-METHYL ESTER: $C_{14}H_{11}O_3N(COOH)(COOCH_3)$. Formed by refluxing papaverinic acid anhydride with methyl alcohol (76). A yellow crystalline powder from benzene, soluble in boiling water, m. p. 156° (75) (77). —γ-METHYL ESTER, from the action of methyl iodide, or of methyl alcohol and sulphuric acid on papaverinic acid; white needles from water, m. p. 196° with loss of CO_2(74). (*Cf.* Wegscheider (78).) —DIMETHYL ESTER, $C_{14}H_{11}O_3N(CO_2CH_3)_2$, formed by heating the β-methyl ester with methyl alcohol and sulphuric acid (74) (75) (*cf.* Schranzhofer (79)), large plates from acetone, m. p. 121° to 122°. —β-ETHYL ESTER, $C_{14}H_{11}O_3N(COOH)(COOC_2H_5)$, from papaverinic acid with alcohol and acetic anhydride, or boiling papaverinic anhydride in absolute ethyl alcohol. White needles, m. p. 187° to 188° (73) (76). —γ-ETHYL ESTER, from papaverinic acid with ethyl alcohol and a few drops of conc. sulphuric acid; white needles, m. p. 184°. Conductivity (135).

PAPAVERINIC ANHYDRIDE: $C_{16}H_{11}O_6N$, formed by boiling papaverinic acid with acetic anhydride. From benzene, needle clumps, m. p. 169° to 170°; sublimes; with water gives the acid again (73) (76).

PAPAVERINIC ACID METHYLBETAINE: $C_{17}H_{15}O_7N+H_2O$ (α-veratroyl-apophyllenic acid), obtained together with its methyl ester and papaverinic-γ-methyl ester from heating papaverinic acid 18 hours at 100° with methyl alcohol and methyl iodide (79). Yellow rhombic plates from water, m. p. 192°. —SILVER SALT, decomp. at 137°. —HYDROCHLORIDE, $(+H_2O)$ m. p. 182° to 184° (decomp.). —PLATINICHLORIDE, Crystalline (decomp. 160°) $(C_{17}H_{15}O_7N\cdot HCl)_2PtCl_4+8H_2O$. —AURICHLORIDE, $C_{17}H_{15}O_7N\cdot HAuCl_4+H_2O$. (74), (75), (81). Heating papaverinic acid methylbetaine with phenol converts it to pyropapaverinic acid methylbetaine through loss of carbon dioxide (75).

PAPAVERINIC ACID KETOXIME: $C_{16}H_{14}O_7N_2$ white needles from absol. alcohol, m. p. 154° to 157°, forms a crystalline hydrochloride (72). Conductivity (136). PAPAVERINIC ACID PHENYLHYDRAZONE, light yellow needles from alcohol, m. p. 190° (50). Conductivity (136).

PAPAVERINIC ACID MONAMIDE: $C_{14}H_{11}O_3N(COOH)(CONH_2)$, from treatment of papaverinic anhydride in benzene with ammonia gas (76), or papaverinic ester with ammonium hydroxide (73); crystalline, forms an ammonium and a silver salt.

ANILOPAPAVERINIC ACID: $C_{14}H_{11}ON(CONHC_6H_5)(COOH)$, —Anilide, from refluxing papaverinic anhydride with aniline. Amorphous; m. p. 119° (76).

NITROPAPAVERINIC ACID (53): $C_{16}H_{12}O_7N(NO_2)+H_2O$, from papaverinic acid in conc. nitric acid; pale yellow needles, m. p. 215° (decomp.). More soluble than papaverinic acid; loses H_2O at 125°. Forms a crystalline silver salt.

PYROPAPAVERINIC ACID: (53), (72), (veratroyl-isonicotinic acid) $C_{15}H_{13}O_5N$, is formed by loss of carbon dioxide from papaverinic acid on melting; from alcohol by dilution with water, white leaflets, m. p. 230°. —HYDROCHLORIDE, orange-red needles $C_{15}H_{13}O_5N\cdot HCl+H_2O$. The Ca, Ba, and Ag salts are crystalline. —PHENYLHYDRAZONE, from alcohol, yellow prisms decomp. 223°, forms a red crystalline hydrochloride. —OXIME, colorless needles, m. p. 226°, forms a crystalline hydrochloride. PYROPAPAVERINIC ACID METHYL ESTER (74), from

methyl alcohol, white needles of m. p. 108°. PYROPAPAVERINIC ACID METHYLBETAINE (75), $C_{16}H_{15}O_5N+3H_2O$, formed by loss of carbon dioxide from papaverinic acid methylbetaine on heating in phenol, or from pyropapaverinic acid heated with sodium carbonate and methyl iodide; from dilute alcohol or water, needles of m. p. 182°. It forms a Platinichloride, $(C_{16}H_{15}O_5N)_2H_2PtCl_6+2H_2O$. The betaine, with barium hydroxide, splits to veratric acid and isonicotinic acid methylbetaine.

N-METHYL ISOPAPAVERINE (82): $C_{21}H_{23}O_4N$, from papaverine methiodide with dilute sodium hydroxide, extracted with benzene. Yellow, monoclinic, hygroscopic crystals, taking carbon dioxide from the air; m. p. 129° to 131°. Dissolves in water, alkaline. With acids, e. g., hydrochloric acid, gives papaverine methochloride; with picric acid N-Methylpapaverinium picrate m. p. 132° to 133°, solidifying and melting again at 175° to 176° (90). N-ETHYLISOPAPAVERINE, prisms melting at 101°: Picrate, m. p. 154° to 155°. N-BENZYL ISOPAPAVERINE, yellow scales m. p. 139° to 140°: Picrate, 192°. N-BUTYL ISOPAPAVERINE (87). N-METHYL BROMOISOPAPAVERINE, yellow crystals from alcohol, m. p. 122°. N-BENZYL BROMOISOPAPAVERINE, yellow needles from alcohol, m. p. 113° (87).

N-METHYLNORPAPAVERINIUM BETAINE: (90), (94)[13] $C_{20}H_{21}O_4N+6H_2O$; prepared by treating papaverine methomethylsulphate with dilute barium hydroxide. It crystallizes from water in yellow cubes, m. p. 60° to 65°, anhydrous, m. p. 251° (decomp.). For structure, see Späth and Epstein (95). —PICRATE, leaflets of m. p. 215°. —CHLORIDE [14] (norpapaverine methochloride), colorless crystals, m. p. 222°, forming a PLATINICHLORIDE [15] $(C_{20}H_{22}O_4NCl)_2PtCl_4+3H_2O$, yellow needles or leaflets melting anhydrous at 213°. —IODIDE (norpapaverine methiodide) $C_{20}H_{22}O_4NI+H_2O$, yellow crystals, m. p. anhydrous ca. 180° (decomp.), giving a MERCURICHLORIDE, colorless hydrated crystals. —DICHROMATE, yellow needles, decomp. at 70°.

N-ETHYLNORPAPAVERINIUM BETAINE (90)[16]: $C_{21}H_{23}O_4N+6H_2O$, light yellow, water soluble, m. p. 66° to 67°, anhydrous 179° to 180°. It may crystallize with alcohol or pyridine, but is obtained solvent-free from chloroform. —CHLORIDE (norpapaverine ethochloride),[17] hydrated crystals, melting anhydrous at 196°. —BROMIDE (norpapaverine ethobromide),[18] $C_{21}H_{24}O_4NBr+4H_2O$, m. p. 61° to 62°, anhydrous 195° to 196°. —PICRATE,[19] m. p. 179° to 180°. —The DICHROMATE (reddish-brown crystals) and IODIDE (yellow crystals) are also known.

N-METHYLHOMOPAPAVERINIUM (90): —IODIDE (homopapaverine methiodide), orange crystals from alcohol, containing 1 molecule C_2H_5OH; alcohol-free it melts at 187° to 188° (decomp.). —BROMIDE (homopapaverine methobromide), amorphous. —PICRATE, m. p. 133° to 134°.

N-ETHYLHOMOPAPAVERINIUM (90): —IODIDE (homopapaverine ethiodide), hydrated, m. p. 221° to 223° (decomp.). —PICRATE, m. p. 126° to 127° (decomp.).

N-PHENACYLNORPAPAVERINIUM BETAINE: Colorless needles m. p. 186° to 187°, is probably the correct name for the phenacyl papaverinium oxide of v. Seutter (133).

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[13] Stransky's papaverine methohydroxide.

[14] Confused by Goldschmiedt (92) and Stransky (91) with papaverine methochloride.

[15] The papaverinium methohydroxide platinichloride of Goldschmiedt (92).

[16] The papaverinium ethohydroxide anhydride of Goldschmiedt and Stransky.

[17] Confused by Stransky with papaverine ethochloride.

[18] May have the same crystalline form as papaverine ethobromide, which led Goldschmiedt and Stransky to consider it identical with this.

[19] The N-ethylpapaverinium picrate of Goldschmiedt and Stransky (91). The papaverine benzohydroxide anhydride described by Stransky is actually N-benzyl dimethoxyisoquinoline (90).

PAVINE (97), (98), (99): $C_{20}H_{23}O_4N+3H_2O$, the tetrahydropapaverine of Goldschmiedt (54) and Pope and Peachy (101). It is formed by reduction of papaverine with tin in hot, very dilute hydrochloric acid. It crystallizes from water or aqueous alcohol as needles, of m. p. 201° to 202°, very soluble in alcohol, chloroform, or carbon disulphide, diff. soluble in ether or petroleum ether (54). It may be purified through the acid oxalate. Crystal measurements, Koechlin (137). Not oxidized by manganese dioxide and sulphuric acid (103). It is optically inactive, but may be resolved into active components: *l*-pavine, efflorescent crystals, m. p. 223° to 224°, in chloroform $[\alpha]_D=-143.4°,-149.5°$; *d*-pavine, m. p. 223° to 224°, in chloroform $[\alpha]_D=+153.7°$, in glacial acetic acid $[\alpha]_D=+198.3°$. A solution of the two forms precipitates the racemic base, melting at 200° to 201° (101). PAVINE SALTS, $B=C_{20}H_{23}O_4N$:—HYDROCHLORIDE, $B\cdot HCl\cdot 5H_2O$, decomp. 325°; $B\cdot HCl\cdot 8H_2O$ and $B\cdot HCl$ are also known (97); $B\cdot HCl\cdot 3H_2O$, monoclinic, decomp. 290°. —PLATINICHLORIDE, $(B\cdot HCl)_2PtCl_4+3H_2O$, yellow microneedles (54). —HYDRIODIDE $B\cdot HI+4H_2O$, hydrated softens at 75°, melts ca. 265°, anhydrous sinters at 195° without melting (99). —ACID SULPHATE, $B\cdot H_2SO_4+7H_2O$, white crystals. —ACID OXALATE, $B\cdot H_2C_2O_4$, white prisms. —DICHROMATE, $B_2\cdot H_2Cr_2O_7$, orange prisms (54). —PICRATE, yellow needles, decomp. 285° (97). The action of methyl iodide on pavine results in N-methylpavine -hydriodide and -methiodide, and traces of pavine hydriodide (99). *l*-PAVINE-*d*-α-BROMOCAMPHORSULPHONATE, colorless needles, m. p. 295° to 298°, in absol. alcohol $[\alpha]_D=-30°$. *l*-PAVINE-*d*-α-CHLOROCAMPHORSULPHONATE, decomp. 300° to 305° (101). N-BENZOYLPAVINE, $C_{20}H_{22}O_4N\cdot COC_6H_5$, colorless prisms, m. p. 234° to 235° (97).

PAVOLINE:[20] (Goldschmiedt's tetrahydropapaveroline (54), Pyman's 1,2-dihydropapaveroline (97)) amorphous, alkali-soluble substance from the action of fuming HCl on pavine at 175°, three hours. —HYDROCHLORIDE, $C_{16}H_{15}O_4N\cdot HCl+\frac{1}{2}H_2O$, colorless prisms decomp. 296°.

N-METHYLPAVINE (99), $C_{21}H_{25}O_4N+2H_2O$, is formed by reduction of papaverine methomethylsulphate with tin and hydrochloric acid. The chief product of this reduction is *d*, *l*-laudanosine (tetrahydro-N-methylpapaverine), of which, however, N-methylpavine does not represent an intermediate step, since it can not be further reduced to laudanosine. N-methylpavine (hydriodide) is the chief product of the action of methyl iodide on pavine. It is likewise formed by oxidation of laudanosine. After dehydration in boiling benzene with sodium sulfate, N-methylpavine crystallizes in anhydrous prisms of m. p. 140° to 141°. —HYDROCHLORIDE, $B\cdot HCl\cdot 8H_2O$ (where B=N-methylpavine=$C_{21}H_{25}O_4N$) colorless prisms, m. p. 65° to 81°. —AURICHLORIDE, terra-cotta colored needles, containing one molecule of alcohol, decomp. 198°. —HYDRIODIDE, $B\cdot HI+6H_2O$ prisms of m. p. 70° to 87°. —PICRATE, m. p. 219°. —METHIODIDE, $B\cdot CH_3I\cdot 2H_2O$, colorless rods, decomp. 280°. —METHOCHLORIDE, $B\cdot CH_3Cl\cdot 7H_2O$, m. p. 75° to 99°. —METHOHYDROXIDE, prisms, decomp. ca. 100° (99).

N-METHYLPAVINEMETHINE (98): $C_{22}H_{27}O_4N\cdot 2H_2O$, from N-methylpavine methiodide with alkali, crystals, becoming amorphous in air. —HYDROCHLORIDE, $C_{22}H_{27}O_4N\cdot HCl\cdot 1\frac{1}{2}H_2O$, m. p. 205° to 206°. —AURICHLORIDE, decomp. 156°. —PICRATE, m. p. 195° to 196°. —METHIODIDE, m. p. 174° to 175°. For the numerous degradation and oxidation products of the methine, see the original.

3,4-DIHYDROPAPAVERINE: $C_{20}H_{23}O_4N$, an isomer of pavine, has been obtained only synthetically (67), (106), (109). An oil, distilling at 200° at 0.001 mm. Conversion to papaverine, Späth and Burger (106); conversion to *d*, *l*-laudanosine, Pictet and Finkelstein (109). —PICRATE, m. p. 168° (67).

[20] This name is here introduced in consistence with Pyman's pavine nomenclature.

1,2-DIHYDROPAPAVERINE (143): $C_{20}H_{23}O_4N$. Synthetic; cryst. from dilute methyl alcohol in narrow hexagonal plates of m. p. 97° to 98°. Color reactions of the base are described. —PERCHLORATE, $C_{20}H_{23}O_4N \cdot HClO_4$, sphaerocrystalline white powder, melts with decomp. at 238°. —PICRATE, m. p. 151°.

TETRAHYDROPAPAVERINE:[21] $B = C_{20}H_{25}O_4N$, is formed by electrolytic reduction of papaveraldine (105) or of papaverine (106), or reduction of the latter with tin and hydrochloric acid (97), or catalytic reduction of 1,2-dihydropapaverine (143); amorphous. —HYDROCHLORIDE, $B \cdot HCl \cdot 4\frac{1}{2}H_2O$, $B \cdot HCl \cdot H_2O$, from absol. alcohol B·HCl, m. p. 217° to 219°. —AURICHLORIDE, $B \cdot AuCl_4$, yellow radially clustered needles, decomp. 176°. —HYDRIODIDE, B·HI, prisms of m. p. 259° to 260°. —PICRATE, yellow irregular prisms, m. p. 161° to 162°. —NITROSAMINE, short needles, of m. p. 135° to 136°. N-METHYLTETRAHYDROPAPAVERINE (*d*, *l*-laudanosine), is obtained by reduction of papaverine methochloride with tin and hydrochloric acid, m. p. 115°. It may be resolved with quinic acid into the optically active antipodes of m. p. 89° (130) (138). (See Laudanosine.) N-BENZOYLTETRAHYDROPAPAVERINE, needle-prisms from absol. alcohol, m. p. 159° to 160°. Bromo derivative, leaflets m. p. 185° to 186° (97). N-ETHYLTETRAHYDROPAPAVERINE (103), $C_{20}H_{24}O_4N \cdot C_2H_5$, from reduction of papaverine ethochloride with tin and hydrochloric acid; white fluffy needles, m. p. 89°, forming a Picrate of m. p. 167° to 170°. For oxidation products see the original. N-PROPYLTETRAHYDROPAPAVERINE, amorphous, forming a Picrate of m. p. 122° to 125° (103). N-METHYLTETRAHYDROAMINOPAPAVERINE (*d*, *l*-aminolaudanosine), m. p. 145° (93). With methyl iodide, tetrahydropapaverine gives its hydriodide and laudanosine methiodide and hydriodide. With conc. hydrochloric acid it forms TETRAHYDROPAPAVEROLINE, $C_{16}H_{17}O_4N$, whose crystalline Hydrochloride decomp. at 291° to 293° (97). Tetrahydropapaverine with palladium-asbestos at 200° loses hydrogen to form papaverine quantitatively (106). It is oxidized by iodine to 3,4-dihydropapaveraldine (65), m. p. 190° to 191°. With acetal, tetrahydropapaverine reacts with ring closure, giving α-coralydine, m. p. 148° and β-coralydine, m. p. 115°. These both dehydrogenate to the same dehydrocoralydine (107). Ring closure with methylal gives norcoralydine, m. p. 157° to 158°, hydrochloride 213°, picrate 138° (108). BROMOTETRAHYDROPAPAVERINE (139), $C_{20}H_{24}O_4NBr$, from reduction of bromopapaverine with tin and hydrochloric acid, crystallizes hydrated, m. p. 71° to 73°, anhydrous 111°.

PAPAVERINE SULPHONIC ACID (145): $C_{20}H_{21}O_7NS$, prep. by treatment of papaverine with conc. H_2SO_4 at 0°. Colorless prisms from hot water, m. p. 301°, decomp.

BROMOPAPAVERINE (3): $C_{20}H_{20}O_4NBr$, from papaverine hydrobromide with bromine water. Monoclinic crystals from alcohol, m. p. 144° to 145° (13). —HYDROCHLORIDE, crystals from alcohol, m. p. 197°. —PICRATE, decomp. 125°. — METHIODIDE, yellow cubes, decomp. ca. 225°. The bromine atom lies in the 6′-position of the veratryl group (87). Reduction, Späth and Lang (139). CHLOROPAPAVERINE, is a resin (3).

NITROPAPAVERINE (3): $B = C_{20}H_{20}(NO_2)O_4N$. From papaverine in conc. nitric acid at 0°, nearly quantitative yield; m. p. 186° to 187°; soluble in 100 to 110 parts hot alcohol, 40 parts ethyl acetate, 3 parts chloroform, 10 parts xylene (93). For preparation, see also Decker, et al. (110). —HYDROCHLORIDE, $B \cdot HCl + 1\frac{1}{2} H_2O$; numerous salts incompletely described by Hesse (10) and by Anderson (3). —METHIODIDE, $B \cdot CH_3I$, from water, m. p. 225°, decomp. 235°. —METHOBROMIDE, $B \cdot CH_3Br$, crystallizes from alcohol, decomp. 227°. —METHOCHLORIDE, $B \cdot CH_3Cl$, from alcohol, m. p. 212°. —METHOMETHYLSULPHATE, $B \cdot (CH_3)_2SO_4$, from water, decomp. 238° (93).

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[21] The isotetrahydropapaverine of Freund and Beck. (105).

NITROSOPAPAVERINE (63): By action of nitrous fumes on boiling chloroform solution of papaverine hydrochloride; m. p. 181.5°, does not give Liebermann's reaction. —HYDROCHLORIDE, m. p. 181°. —NITRATE, 183°. —PLATINICHLORIDE, 235°. —PICRATE, 120°.

AMINOPAPAVERINE: $C_{20}H_{20}O_4N(NH_2)+C_2H_5OH$, by reduction of the nitro compound. M. p. 116°, alcohol-free 143°. Acetyl derivative, crystallizes with one molecule of benzene, m. p. 125°, solvent-free 162°. AMINOPAPAVERINE METHOCHLORIDE, has the m. p. 147°, and forms a hydrochloride of m. p. 200°. DIAZOPAPAVERINE, colorless crystals from alcohol, m. p. 281°, forming a methiodide decomp. at 198°, and a methomethylsulphate of m. p. 168° to 169° (93).

PHENANTHRENO-N-METHYLTETRAHYDROPAPAVERINE: (*d,l*-glaucine) from the diazo compound of N-methyltetrahydroaminopapaverine, oily, forms a methiodide of m. p. 215° (93). According to Gadamer (111) this is *d,l*-laudanosine methiodide, and *d,l*-glaucine methiodide which is also contained in the reaction mixture has the m. p. 224° to 226°.

METHYLENEPAPAVERINE: $C_{21}H_{21}O_4N$, is formed by heating papaverine with conc. formaldehyde solution in a sealed tube, 28 hours at 100°; colorless needles from absol. alcohol, m. p. 155° to 156°. —HYDROCHLORIDE, m. p. 110°, decomp. at 130° to 140°. —HYDROBROMIDE, m. p. 110°, decomp. at 120°. —PICRATE, sinters at 100°, m. p. 115° (115). The base may be reduced with catalytic hydrogen to DIHYDROMETHYLENEPAPAVERINE, $C_{21}H_{23}O_4N$, m. p. 154° (18).

7-DEMETHYLOMETHYLPAPAVERINOL: $C_{20}H_{21}O_5N$, is formed by the action of excess of methyl magnesium iodide on the carbonyl group of papaveraldine; m. p. 114° to 116°. On warming with 50% sulphuric acid, it forms ANHYDRO-7-DEMETHYLOMETHYLPAPAVERINOL, $C_{20}H_{19}O_4N$, m. p. 151°, which yields a PICRATE of m. p. 110° to 112° and a PERCHLORATE of m. p. 150°. The above-mentioned bases do not behave as phenols. On reduction with tin and hydrochloric acid they yield 7-DEMETHYLOMETHYLPAPAVERINE, $C_{20}H_{21}O_4N$, m. p. 148°, and further reduction gives 7-DEMETHYLOMETHYLTETRAHYDROPAPAVERINE, $C_{20}H_{25}O_4N$, m. p. 64° to 65°, which forms a PICRATE, decomp. at 225°, and a NITROSAMINE of m. p. 124°. The tetrahydro base condenses with methylal to give a 7-demethylopseudocorydaline (70).

PROTOPAPAVERINE (63) (116) (trimethylpapaveroline): $C_{17}H_{13}(OCH_3)_2O_2N$, is formed in 41% yield when papaverine hydrochloride is heated to 235°.[22] It separates from alcohol in yellowish crystals melting at 279° to 280° and forms a (hydrated) HYDROCHLORIDE of m. p. 66° to 67° (116), melting anhydrous at 200° (17), $B{\cdot}HCl+5H_2O$ (where $B=C_{19}H_{19}O_4N$). —PLATINICHLORIDE, $(B{\cdot}HCl)_2PtCl_4+5H_2O$, an orange crystalline powder, decomp. 231°. —MERCURICHLORIDE, decomp. 155°. —HYDROBROMIDE, $B{\cdot}HBr+5H_2O$, pale yellow octahedral crystals. —Hydriodide, $B{\cdot}HI+3H_2O$, brownish-yellow prisms, diff. soluble in water. —ACID OXALATE, $B{\cdot}H_2C_2O_4+5H_2O$, yellow octahedra, melting anhydrous at 138°. The NITRATE is also crystalline. —PICRATE, m. p. 206.5°. —METHIODIDE, 63° to 64°. —METHOCHLORIDE, 70° to 71° (63). With potassium hydroxide a solid potassium derivative may be obtained (17). The sodium salt melts 160° to 175° (63).

OPIANYLPAPAVERINE (117): From condensation of papaverine with opianic acid in the presence of 86% H_2SO_4; m. p. 168° to 170°. HYDROCHLORIDE ($+H_2O$ decomp. 167°.

METHYLENE-DI-PAPAVERINE (117): From condensation with formaldehyde, m. p. 204° to 206°. —HYDROCHLORIDE, $+2H_2O$, crystalline.

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[22] By loss of CH_3Cl and H_2O, apoprotopapaverine is also formed (17). (*Cf.* Fehling-Hell, Neues Handworterbuch der Chemie, vol. 4, p. 1131, ca. 1888.)

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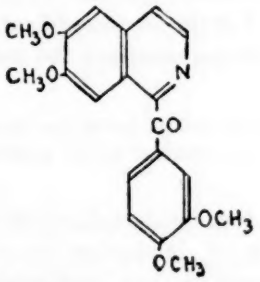
XANTHALINE

Xanthaline, $C_{20}H_{19}O_5N$, which is now known to be identical with papaveraldine, was first isolated in the laboratories of T. and H. Smith and Co. (1) in 1881. It was found in small amounts in the acid mother liquors from the precipitation of morphine and codeine hydrochlorides in the Robinson-Gregory process.

Smith and Co. reported the base as melting at 206° and forming intensely yellow salts; the base takes its name from the last-named property. Analysis of the base and its hydrochloride gave the empirical formula $C_{37}H_{36}O_9N_2$. By reduction of xanthaline in dilute sulphuric acid with zinc, a well-crystallized hydroxanthaline of m. p. 137° was obtained, which on analysis gave values corresponding to the formula $C_{37}H_{38}O_9N_2$.

In a subsequent investigation of samples of xanthaline from the T. and H. Smith factory, Dobson and Perkin (2) showed that the base purified from methyl ethyl ketone melts at 207° (210° corr.), contains 4 methoxyl groups, and gives analyses corresponding to $C_{20}H_{19}O_5N$. On fusion with potassium hydroxide, it yields dimethoxyisoquinoline and veratric acid. The properties of xanthaline and its salts agree with those of the base papaveraldine (p. 7), an oxidation product of papaverine (3). Direct comparison of xanthaline with papaveraldine showed them to be identical in every respect. Xanthaline is therefore to be represented by the following papaveraldine structural formula:



Xanthaline (Papaveraldine)

Descriptive Part

XANTHALINE HYDROCHLORIDE ($C_{37}H_{36}O_9N_2.2HCl+4H_2O$) consists of yellow needles. The sulphate also crystallizes in yellow needles (1). XANTHALINE PLATINICHLORIDE $(C_{20}H_{19}O_5N.HCl)_2PtCl_4$ crystallizes from dilute hydrochloric acid in orange-red prisms (2). XANTHALINE METHIODIDE, $C_{20}H_{19}O_5N.CH_3I+3H_2O$, orange starlike crystals, m. p. 132°. On recrystallization from methyl alcohol it separates in brilliant yellow prisms, $C_{20}H_{19}O_5N.CH_3I+H_2O$, of m. p. 194° (2). XANTHALINE PICRATE, cryst. from 90% alcohol, melts at 212.5° (corr.) (4). HYDROXANTHALINE ($C_{37}H_{38}O_9N_2$), from reduction of xanthaline with zinc in dilute sulphuric acid; colorless anhydrous crystals, nearly insol. in water, very soluble in alcohol or benzene. It gives colorless, well crystallized salts (1). (See Papaveraldine, p. 19.)

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LAUDANOSINE

Laudanosine was found by Hesse (1) (1871) in opium, where it occurs only in traces (ca. 0.0008%). Its separation from morphine-extraction mother liquors is difficult; of the long series of alkaloids it is the last to come out (2) (3).

The alkaloid has the empirical formula $C_{21}H_{27}O_4N$. It separates in needles from ligroin, prisms from alcohol. It is soluble in hot ligroin

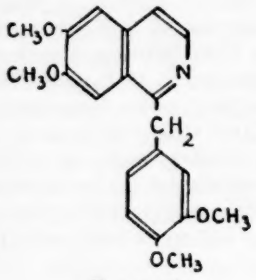
or petroleum ether, very soluble in alcohol or chloroform, in ether (16°) 1:19.3 (1) (2). It is insoluble in water [23] or alkali (2) (very slightly soluble in dil. ammonia), but dissolves in acids with salt formation. Its alcoholic solution reacts strongly alkaline, and tastes bitter; the salts are exceedingly bitter (2). The base melts at 89° and begins to decompose at about 110°; it does not sublime (2).

In conc. sulphuric acid, laudanosine gives a rose coloration (2), which disappears on warming; above 100° it passes through greenish-gray to violet at 130° (4). With Fröhde's reagent, pink-violet; Mandelin's reagent, red-brown; Lafon's reagent, purple-red, becoming brown (4). With the Magnol test (David (5)) it forms a lilac (Rosazurin G) ring.

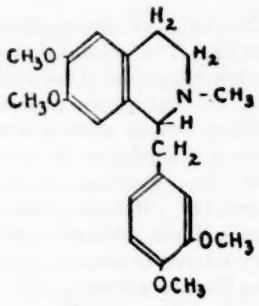
Laudanosine is dextrorotatory, $[\alpha]^{15} = +103.23°$, $[\alpha]^{22.5} = +105°$, in 97 per cent alcohol (6). For the levo-modification (obtained by resolution of N-methyltetrahydropapaverine) the rotation $[\alpha]_D^{15} = -105.42°$ was found (4).

The absorption spectra of the group, laudanine, laudanosine, and laudanidine, are closely related, and are very similar to the spectra of tetrahydropapaverine and corydaline (7).

Laudanosine contains four methoxyl groups, and a tertiary nitrogen atom. The relationship of laudanine to papaverine (8) and to laudanosine (2) (9) suggested that laudanosine must be N-methyltetrahydropapaverine, which was confirmed by experiment. (Pictet and Athanasescu (4).)



Papaverine



Laudanosine

Papaverine methochloride, reduced with tin and hydrochloric acid, yielded a base $C_{21}H_{27}O_4N$, of m. p. 115° [24] and identical chemically with laudanosine. By resolution with quinic acid the optical antipodes were obtained. The *d*- form, because of difficulty of purification of the quinic acid salt, had a rotatory power somewhat less than that of natural laudanosine; the *l*- form showed the expected rotation, and formed with opium laudanosine the racemic base melting at 115°.

Reduction of papaverine methosulphate gives somewhat better yields of r-laudanosine (10).

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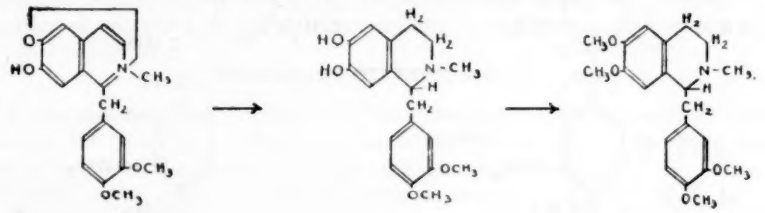
[23] N-methyltetrahydropapaverine (racemic laudanosine) is slightly soluble in boiling water and crystallizes out on cooling (4).

[24] Apparently the same substance (m. p. 113°) was obtained by Kauder (3) (1890) by methylation of laudanine but was not recognized as racemic laudanosine.

Papaverine has also been converted to r-laudanosine (Pyman (11)) by reducing to tetrahydropapaverine, whose methiodide is identical with r-laudanosine hydriodide.

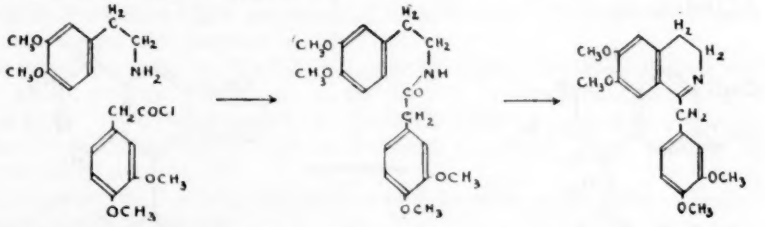
By another variation (Späth and Epstein (12)) protopapaverine (from the melt of papaverine hydrochloride) was reduced with tin and hydrochloric acid, and the product methylated to *d, l*-laudanosine; or protopapaverine may be first converted to its methiodide, the latter reduced, and the product (racemic codamine) methylated to *d, l*-laudanosine. (See Papaverine and Codamine.)



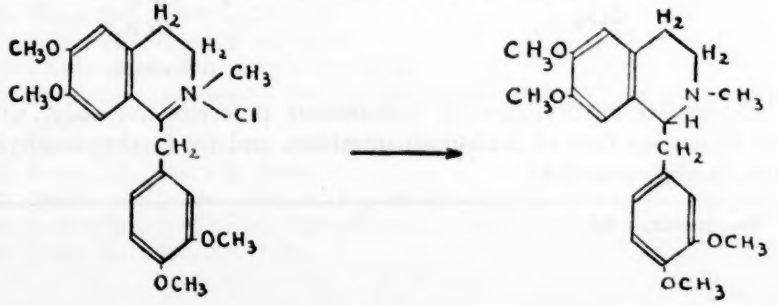
Protopapaverine Laudanosine

The formation of r-laudanosine by methylation of laudanine (3), (9) (most advantageously with diazomethane (13)) should be mentioned here.

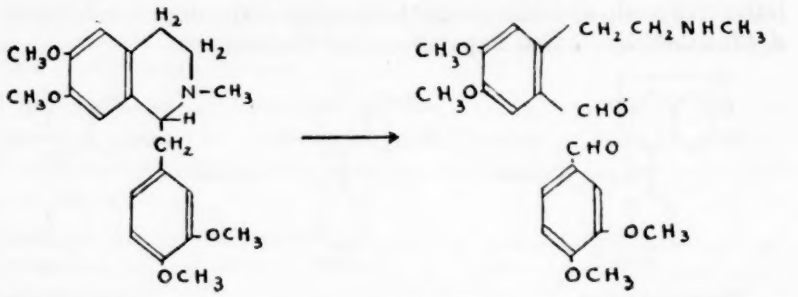
The first complete synthesis of laudanosine was carried out by Pictet and Finkelstein (14) (1909), which has a particular interest as the first synthesis of an opium alkaloid. Homoveratrylamine and homoveratroyl chloride were condensed, and the product treated with phosphorous pentoxide, whereby a dihydroisoquinoline ring was closed through loss of water.



The 3,4-dihydropapaverine so formed, by conversion to the methochloride and subsequent reduction, gave racemic laudanosine.

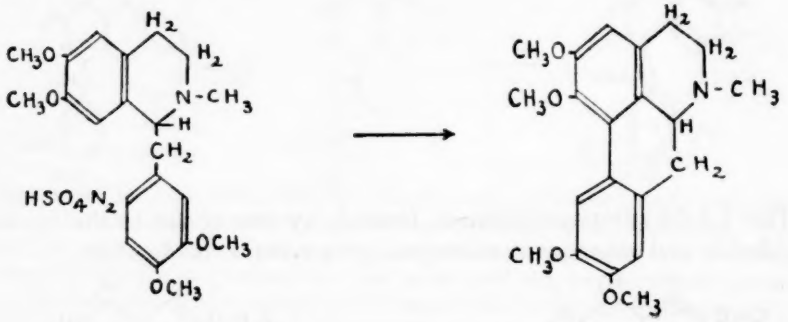


The accepted laudanosine formula rests largely on synthesis and relationships to papaverine; comparatively little structural determination has been done on the natural alkaloid itself. By oxidation with manganese dioxide (Pyman(15)) or mercuric acetate (Gadamer and Kondo(16)) are obtained veratraldehyde and 4,5-dimethoxy-2-(β-methylaminoethyl)-benzaldehyde. The latter is an analog of cotarnine, which it closely resembles in properties.*



Like cotarnine, it forms colored salts with closure of a dihydroisoquinoline ring. The hydrochloride is identical with 6,7-dimethoxy-3,4-dihydroisoquinoline methochloride (11). Treatment of the salts with aqueous KCN yields a colorless cyanide, the analog of cotarnine cyanide. With alkali or acetone the aldehyde shows the typical reactions of an aromatic aldehyde.

Through its amino derivative, laudanosine has been related to r-glaucine (Pschorr (17), Gadamer (18)). r-Laudanosine diazonium sulphate, in the presence of copper powder, forms by internal condensation r-glaucine, or by the usual diazonium decompositions r-laudanosine, r-hydroxylaudanosine, and the dimolecular product, r-dilaudanosine.



r-Glaucine

Exhaustive methylation of laudanosine proceeds normally, with the formation first of laudanosinemethine. and by further methylation, laudanosene (19).

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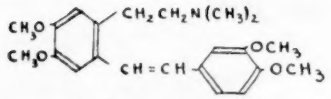
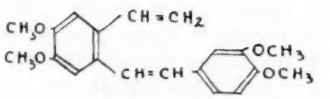
*See Appendix, p. 357.



Laudanosinemethine



Laudanosene

Laudanosoline, a demethylated laudanosine, results from the action of aluminum chloride on laudanosine (20). The four methoxyl groups are converted to hydroxyl, but the methylimido group is untouched.

By ethylation and carbethoxylation of the hydroxyl group of laudanine, ethyl laudanosine and carbethoxyl laudanosine, respectively, have been prepared (13).

A laudanosine type, containing the methylenedioxyl group, results from condensation of cotarnine with 6-nitrohomoveratrol and subsequent elimination of the nitro group (21).

Descriptive Part (Laudanosine)

d-LAUDANOSINE: B=$C_{21}H_{27}O_4N$. —HYDRIODIDE, B·HI+½H_2O, diff. sol., used to isolate the base (1). —HYDROCHLORIDE, amorphous (2). —NEUTRAL OXALATE, amorphous; Acid oxalate, prisms, B·$C_2H_2O_4$+3H_2O (2).

l-LAUDANOSINE (4). —QUINATE, colorless needles, m. p. 120°, $[\alpha]_D$= −96.74°.

d,l-LAUDANOSINE (4): Salts very soluble in water and crystallize with difficulty. —HYDROCHLORIDE, white powder of m. p. ca. 123°. —HYDRIODIDE, m. p. 201° to 203° (11). —PLATINICHLORIDE, microcrystals decomp. 160° (4). —AURICHLORIDE, m. p. 164° (14). —MERCURICHLORIDE, white crystals m. p. 172° (4) —PICRATE, yellow plates m. p. 174° (175°) (14). —METHIODIDE, m. p. 215° to 217°, recryst. from alcohol (4) (11). —ETHIODIDE, m. p. 202° to 203° (4).

d,l-AMINOLAUDANOSINE (17) (18), m. p. 145°. *d,l*-DILAUDANOSINE, is a dimolecular product from diazotized aminolaudanosine. *d,l*-HYDROXYLAUDANOSINE, m. p. 189° to 190.5° (18); salts described.

LAUDANOSOLINE: Prep. by heating dry laudanosine for 20 min. with $AlCl_3$ at 160° to 165°, and treating with ice and H_2SO_4; white crystals of the sulphate, $(C_{17}H_{19}O_4N)_2H_2SO_4$+4$H_2O$, are obtained in 85% yield. The sulphate loses its crystal water at 125°, melts at ca. 230° (20).

LAUDANOSINEMETHINE: $C_{22}H_{29}O_4N$, prep. by boiling laudanosine methiodide with alkali; colorless needles, m. p. 96° to 97°. —HYDROCHLORIDE (+H_2O), m. p. 220°. —HYDROBROMIDE, m. p. 214°; Hydrobromide mercuribromide, yellow needles m. p. 169° to 170°. —PICRATE, m. p. 181° (from benzene 106° to 112°, cont. solvent) (19).

LAUDANOSENE: $C_{20}H_{22}O_4$, end product of exhaustive methylation of laudanosine; m. p. 94° to 95° (19).

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LAUDANINE

Laudanine is found in the alkaline mother liquors from morphine extraction, in amounts corresponding to about 0.005% of the opium employed; it was isolated and characterized by Hesse (1) (2) in 1870. (See also Kauder (3).)

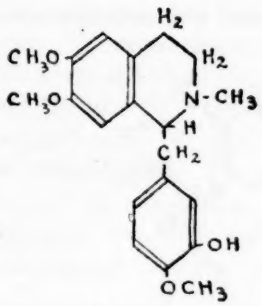
The base crystallizes from alcohol or chloroform in colorless rhombic prisms (4), of melting point 166° to 167° (5) (6); density 1.256 (7). It does not sublime (2). It is soluble in benzene, chloroform, or hot alcohol, sparingly soluble in cold alcohol, or ether (1 in 647 parts at 18°) (5). For absorption spectrum, see Dobbie and Lauder (8).

Laudanine reacts basic, and forms a series of well-defined salts; it is precipitated from solutions of its salts by alkali, and redissolves in excess of the reagent.[25] The presence of a phenolic hydroxyl group is indicated by a color reaction with ferric chloride. With conc. H_2SO_4 the base gives a red color, becoming reddish violet at 150° (1).

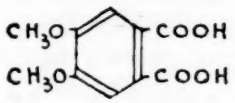
Although the alkaloid has an asymmetric carbon atom, it is optically inactive (4). Like several other inactive alkaloids, it was at first reported to be weakly levorotatory (9); the rotation was later found to be due to traces of laudanidine (10). It is rare that an asymmetric molecule occurs in living organisms in the inactive state;[26] in this case the plant seems to have synthesized the racemic base. The formation of laudanine by racemization of active material during the purification process does not come into question, since it has not been possible to racemize laudanidine (naturally occurring *l*-laudanine) by the most drastic treatment (6). (*Cf.* Hess. (11).)

Laudanine has the empirical formula $C_{20}H_{25}O_4N$ and is isomeric with tetrahydropapaverine. It contains one hydroxyl group and three methoxyls. The nitrogen is tertiary. The relationships to papaverine and to laudanosine show its structural formula to be:

[25] It may, however, be extracted from its dilute ammoniacal solution with chloroform (2).
[26] For a discussion of known cases, see Hess and Weltzien (11), *cf.* Pringsheim (12), Hess (13).



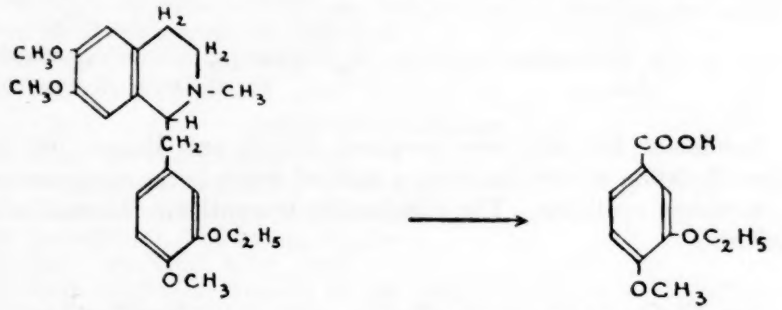
Laudanine



Metahemipinic Acid

By oxidation with alkaline permanganate, Goldschmiedt (4) obtained metahemipinic acid, proving that the phenolic hydroxyl group is not in the isoquinoline nucleus.

The first attempts at methylation (Kauder (3), Hesse (14)) yielded only small amounts of racemic laudanosine; reaction with ethyl iodide gave an ethyllaudanine. By treatment of laudanine with diazomethane, r-laudanosine is obtained in good yields (15). The position of the hydroxyl group was determined by ethylation and subsequent oxidation (Späth (15)), whereby 3-ethoxy-4-methoxy benzoic acid (identified by synthesis from isovanillic acid) was obtained:



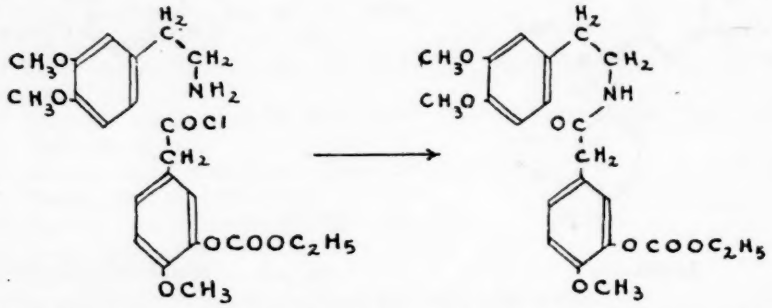
Ethyllaudanine

3-Ethoxy-4-Methoxy Benzoic Acid

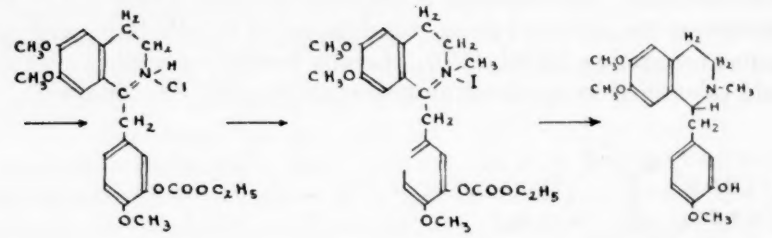
By a similar protection of the hydroxyl group with $-COOC_2H_5$ and oxidation, carbethoxyisovanillic acid is formed, which hydrolyzes to isovanillic acid (15).

The synthesis of laudanine was accomplished by Späth (16), using the Bischler-Napieralski (17) (18) isoquinoline ring closure already employed by Pictet and Finkelstein (19) in the laudanosine synthesis.

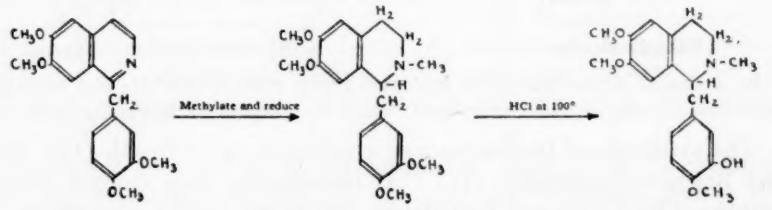
Homoveratryl amine (from isovanillin) was condensed with carbethoxyhomoisovanilloyl chloride:



The product of this condensation, on heating in toluene with phosphorous pentoxide, underwent ring closure to 1-(carbethoxyisovanilloyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride. This was converted to the methiodide, methochloride, and then treated with tin and hydrochloric acid, whereby the dihydroisoquinoline group was reduced to the tetrahydro derivative, with simultaneous hydrolysis of the carbethoxyl group. The product was identical with natural laudanine.



Laudanine has also been prepared (Späth and Burger (6)) by demethylation of r-laudanosine, a method which is the equivalent of a complete synthesis. The relationship to synthetic material is as follows:



Papaverine r-Laudanosine Laudanine

By resolution of r-laudanosine and demethylation of the optical antipodes, *l*-laudanine (natural laudanidine) and the new *d*-laudanine were obtained. Combination of these likewise produced natural inactive laudanine.

Two phenolic isomers of laudanine are known. Isolaudanine (m. p. 76°) was obtained (Pictet and Kramers (20)) by reduction of

"trimethylpapaveroline" methochloride with tin and hydrochloric acid. Trimethylpapaveroline is identical with protopapaverine (3′, 4′-dimethylpapaveroline-N-methyl-6-betaine), from which Späth and Epstein (21), by the procedure of Pictet and Kramers, obtained rac. codamine (an oil), an isomer of laudanine and perhaps the same as isolaudanine. Pseudolaudanine (Decker and Eichler (22)) is formed by reduction of N-methylnorpapaverinium betaine. Its structure has been shown by Späth and Epstein (21) (23). (See Codamine.)

Descriptive Part (Laudanine)

LAUDANINE: B=$C_{20}H_{25}O_4N$. —HYDROCHLORIDE, B·HCl+$6H_2O$, colorless prisms, sol. in water, alcohol. —HYDROBROMIDE, B·HBr+$2H_2O$. —SULPHATE, colorless crystals. —ACID SULPHATE, B·H_2SO_4+$4H_2O$. —OXALATE colorless crystals. —ACID OXALATE, B·$C_2H_2O_4$+$6H_2O$, colorless prisms, m. p. ca. 110°, sparingly soluble in cold water. —ACID TARTRATE, B·$C_4H_4O_6$+$3H_2O$, clumps of prisms from water, m. p. 100°. —PLATINICHLORIDE, $(B\cdot HCl)_2PtCl_4$+$2H_2O$, decomp. above 100°. —AURICHLORIDE, yellow, amorphous, decomp. by boiling water (1) (2) (5). —PICRATE (16), m. p. 176° to 177°. —SODIUM SALT, $C_{20}H_{24}O_4NNa$+$4H_2O$ (14).

CARBETHOXYLAUDANINE (16). —PLATINICHLORIDE $(C_{23}H_{27}O_6N\cdot HCl)PtCl_4$.

ETHYLLAUDANINE (14) (15). —HYDROCHLORIDE, $C_{22}H_{29}O_4N\cdot HCl$+$5H_2O$. —PLATINICHLORIDE is known. The free base is amorphous.

ISOLAUDANINE (20), From reduction of papaverine methochloride; m. p. 76°; soluble in alkali but not in sodium carbonate; green ferric chloride reaction; H_2SO_4, no color; H_2SO_4+$FeCl_3$, blue; Fröhde's reagent, blue; Lafon's reagent, blue; Mandelin's reagent, greenish-yellow.

PSEUDOLAUDANINE (21) (22): $C_{20}H_{25}O_4N$, from alcohol, m. p. 111° to 112°. —PICRATE, m. p. 162° to 163°.

Bibliography (Laudanine)

(1) Hesse, Ber. **4**, 693 (1871).
(2) Hesse, Ann. **153**, 47 (1870).
(3) Kauder, Arch. Pharm. **228**, 419 (1890).
(4) Goldschmiedt, Monatsh. 13, 691 (1892).
(5) Hesse, Ann. suppl. **8**, 261 (1872).
(6) Späth and Burger, Monatsh. **47**, 733 (1926).
(7) Schröder, Ber. **13**, 1075 (1880).
(8) Dobbie and Lauder, J. Chem. Soc. **83**, 626 (1903).
(9) Hesse, Ann. **176**, 189 (1875).
(10) Hesse, Ann. **282**, 208 (1894).
(11) Hess and Weltzien, Ber. **53**, 119 (1920).
(12) Pringsheim, Ber. **53**, 1372 (1920).
(13) Hess, Ber. **53**, 1375 (1920).
(14) Hesse, J. prakt. Chem. **65**, 42 (1902).
(15) Späth, Monatsh. **41**, 297 (1920).
(16) Späth and Lang, Monatsh. **42**, 273 (1921).
(17) Bischler and Napieralski, Ber. **26**, 1903 (1893).
(18) Decker and Schüler, Ann. **395**, 299 (1912).
(19) Pictet and Finkelstein, Ber. **42**, 1979 (1909); Arch. Sci. phys. nat. (4) **29**, 245 (1910).
(20) Pictet and Kramers, Arch. Sci. phys. nat. (4) **15**, 121 (1903).

(21) Späth and Epstein, Ber. **61**, 334 (1928).
(22) Decker and Eichler, Ann. **395**, 377 (1913).
(23) Späth and Epstein, Ber. **59**, 2791 (1926).

LAUDANIDINE (*l*-LAUDANINE).

Hesse (1), searching for the optically active impurity associated with laudanine, discovered a new alkaloid, $C_{20}H_{25}O_4N$, which he named laudanidine because of its great similarity to laudanine. Hesse found it strongly levorotatory and surmised that it was an optically active form of laudanine (1894).

Laudanidine, in respect to crystalline form, solubility, and behavior with conc. sulphuric acid, ferric chloride, or alkali, is identical with laudanine. It melts at 184° to 185° (2) (Hesse, 177°); $[\alpha]_D^{18} = -100.6°$, $[\alpha]_D^{17} = -90.6°$ (3),[27] (Hesse, $[\alpha] = {}^{15}_{D} -87.8°$) in chloroform. Its salts closely resemble those of laudanine, with the exception of the hydrochloride, which is much more soluble and permits the separation of the two alkaloids.

The Zeisel determination of Hesse showed that there were three methoxyl groups in the molecule. Alkali-solubility and the ferric chloride reaction indicated the presence of a phenolic hydroxyl. Acetylation gave acetyllaudanidine, which still contained the free hydroxyl group and was no longer a base (1).

The structure of laudanidine was demonstrated by Späth and Bernhauer (2). Treatment with diazomethane converted it to the levo- form of laudanosine. The establishment of this relationship left only the position of the hydroxyl group unsettled. This was located, as in the case of laudanine, by ethylation and oxidation; the formation of 3-ethoxy-4-methoxy benzoic acid gave proof that the hydroxyl had the same position as in laudanine.

The synthesis of laudanidine was carried out by Späth and Burger (4). Laudanosine was prepared and resolved by the method of Pictet and Finkelstein, and the *l*-laudanosine thus obtained heated to 100° with hydrochloric acid. The methoxyl group in the 3′-position was converted to hydroxyl; the resulting product was identical with natural *l*-laudanidine. By the same treatment of *d*-laudanosine, *d*-laudanidine was prepared. The enantiomers combined to form natural laudanine, thus settling the relationships of these alkaloids.

A study by Späth and Seka (3) of the alkaloid Tritopine, isolated by Kauder (5) in 1890, has shown it to be laudanidine.

Descriptive Part (Laudanidine)

LAUDANIDINE: $B = C_{20}H_{25}O_4N$ (1). —HYDRIODIDE, B·HI, crystallizes from water. — ACID OXALATE, $B \cdot C_2H_2O_4 + 2H_2O$. —PLATINICHLORIDE, $(B \cdot HCl)_2 PtCl_4 + 4H_2O$.

ACETYL LAUDANIDINE (1): $C_{20}H_{24}(C_2H_3O)O_4N + H_2O$, from alcohol, m. p. 98°; alkali-soluble.

d-LAUDANIDINE (4), m. p. 184° to 185°, $[\alpha]\ {}^{17}_{D} = -94.8°$ in chloroform.

[27] These determinations were carried out on very small amounts of material, and published only as preliminary values.

Bibliography (Laudanidine)

(1) Hesse, Ann. **282,** 208 (1894).
(2) Späth and Bernhauer, Ber. **58,** 200 (1925).
(3) Späth and Seka, Ber. **58,** 1272 (1925).
(4) Späth and Burger, Monatsh. **47,** 733 (1926).
(5) Kauder, Arch. Pharm. **228,** 419 (1890).

CODAMINE

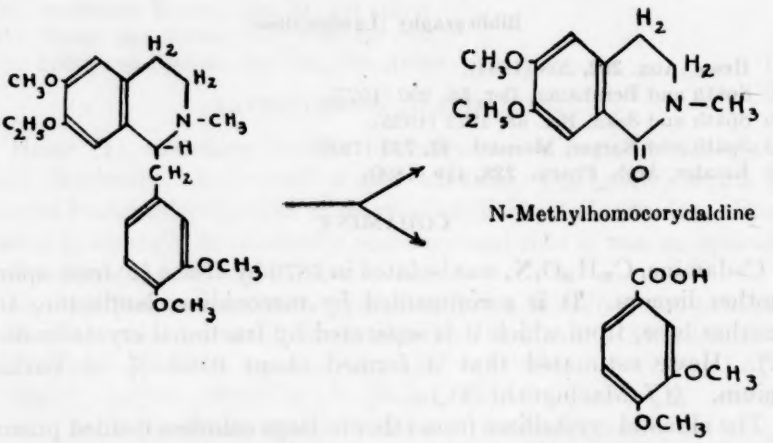
Codamine, $C_{20}H_{25}O_4N$, was isolated in 1870 by Hesse (1) from opium mother liquors. It is accompanied by meconidine, laudanine, and another base, from which it is separated by fractional crystallization (2). Hesse estimated that it formed about 0.0033% of Turkish opium. (*Cf.* Machiguchi (3).)

The alkaloid crystallizes from ether in large colorless 6-sided prisms; it is very soluble in alcohol, from which it separates in well-formed crystals; very soluble in chloroform or ligroin, and somewhat soluble in boiling water. Crystallized from ether or alcohol, it melts at 121°, whereas purified from ligroin it shows the m. p. 126° (2) (4). Heated higher, it browns and decomposes without subliming.

In solution, codamine reacts strongly basic, and forms salts which are mostly amorphous; the salts are bitter in taste, whereas the base is tasteless. The base precipitates amorphous on addition of alkali to the salts, and redissolves in an excess of alkali. With very concentrated alkali, an amorphous precipitate is thrown out, probably the alkali salt (2).

The dark green color shown with ferric chloride indicates the presence of a phenolic hydroxyl group. The solution of the base in conc. nitric acid is dark green, becoming slowly lighter; conc. sulphuric acid gives a colorless solution, which on warming becomes green, then violet (150°).

In addition to a phenolic hydroxyl group, codamine contains three methoxyl groups (5). On methylation it gives *d*-laudanosine; the formula must therefore be $C_{17}H_{15}(OH)(OCH_3)_3N$, with a structure very similar to that of laudanosine. The position of the hydroxyl was determined by ethylating and oxidizing; the products, veratric acid, and the methyl-ethyl ether of nor-m-hemipinic acid proved that the hydroxyl did not lie in the benzyl group, and that it might have either the 6- or 7- position in the isoquinoline nucleus. By gentle oxidation of the ethylated codamine, an N-methylhomocorydaldine

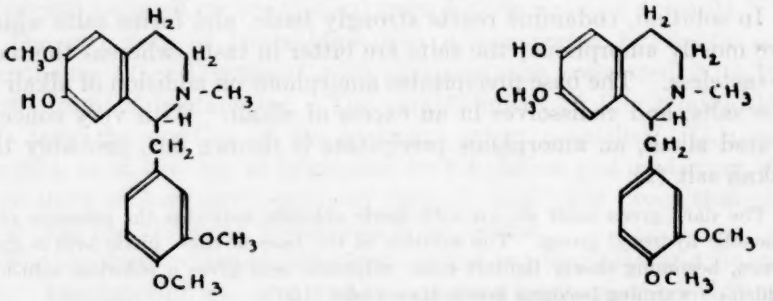


Ethylcodamine

N-Methylhomocorydaldine

Veratric Acid

having the above structure (identified by synthesis) was obtained whereby the hydroxyl of codamine was definitely fixed in the 7-position (5):

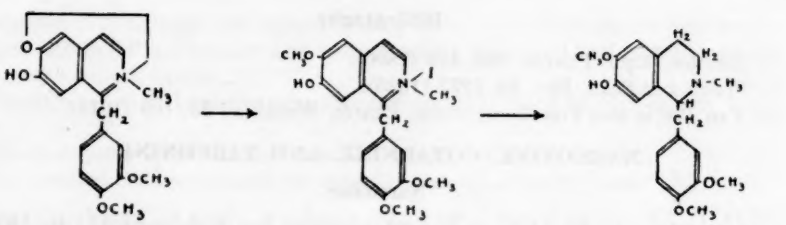


Codamine

Pseudolaudanine

Isomeric with codamine is pseudolaudanine (6), which is formed by reduction of N-methylnorpapaverinium betaine (7). By an application of the above-described methods, pseudolaudanine was shown to have the hydroxyl in the 6-position. Like codamine, it gives r-laudanosine on methylation (8) (5).

The synthesis of *d,l*-codamine was carried out by Späth and Epstein (8), starting from protopapaverine. The constitution of the latter was established by methylation to N-methylnorpapaverinium betaine, the relationship of which to pseudolaudanine has been mentioned above. Protopapaverine, on treatment with methyl iodide, gives an O-methyl ether methiodide (general reaction of phenol-betaines; compare N-methylnorpapaverinium betaine). By converting this methiodide to the methochloride and reducing, racemic codamine was obtained:



Protopapaverine r-Codamine

All attempts to resolve racemic codamine have been unsuccessful.

Descriptive Part (Codamine)

CODAMINE: B=$C_{20}H_{25}O_4N$. —HYDROCHLORIDE, amorphous. —HYDRIODIDE, B·HI+1½ H_2O, white crystals, diff. sol. cold water. —ACID TARTRATE, colorless needles. —PICRATE, amorphous. —PLATINICHLORIDE, $(B\cdot HCl)_2$ $PtCl_4+2H_2O$ (2).

d, *l*-CODAMINE: (8) —PICRATE, m. p. (in vacuum) 187° to 188°.

Bibliography (Codamine)

(1) Hesse, Ann. **153**, 47 (1870).
(2) Hesse, Ann. suppl. **8**, 261 (1872).
(3) Machiguchi, J. Pharm. Soc. Japan, No. **529**, 185 (1926).
(4) Hesse, Ber. **4**, 693 (1871).
(5) Späth and Epstein, Ber. **59**, 2791 (1926).
(6) Decker and Eichler, Ann. **395**, 377 (1913).
(7) Decker and Eichler, Ann. **358**, 288 (1908).
(8) Späth and Epstein, Ber. **61**, 334 (1928).

TRITOPINE

Tritopine was isolated by Kauder (1) in 1890 out of the mother liquors from the crystallization of protopine binoxalate. The pure base was observed to melt at 182°, and gave analytical results leading to the formula $C_{42}H_{54}O_7N_2$. On the basis of the alkali-solubility and color reactions of tritopine, Kauder believed it to be related to laudanine or laudanosine, and suggested that it might be a desoxylaudanosine, formed by union of two molecules of laudanosine with loss of an atom of oxygen.

A recent study of a sample of tritopine which probably was one of the original preparations of Kauder was carried out by Späth and Seka (2). The true formula was determined as $C_{20}H_{25}O_4N$, and the substance proved to be in all respects identical with the alkaloid laudanidine (p. 38). The melting point (evacuated tube) of the pure base lies at 184°, and the rotatory power in chloroform is $[\alpha]_D^{18} = -85.7°$.

The salts of tritopine described in Kauder's work are the Hydrobromide, Hydriodide, Nitrate, Acetate, Sulphate, Binoxalate, Aurichloride, and Platinichloride.

The microchemical reactions of tritopine are described by Van Itallie and Von Toorenburg (3).

Bibliography

(1) Kauder, Arch. Pharm. **228,** 419 (1890).
(2) Späth and Seka, Ber. **58,** 1272 (1925).
(3) Van Itallie and Von Toorenburg, Pharm. Weekblad **55,** 169 (1918).

NARCOTINE, COTARNINE, AND TARCONINE

Narcotine

Narcotine, $C_{22}H_{23}O_7N$, was first isolated by Robiquet (1) in 1817, by exhaustive extraction of opium with ether. It occurs as the free base (2) in opium in widely varying amounts (0.75 to 10%) (3) (4) (5), but may sometimes be entirely lacking.

It is the first alkaloid to appear in the poppy plant, and may be detected three days after the seeds have sprouted; unsprouted poppy seeds are alkaloid-free (6). The mother liquors from morphine production contain narcotine in considerable quantities. It may be separated by precipitation with ammonia and purification of the precipitate with alcohol (7). (Compare Hesse (8), Missenden (9), Dott (10), Kanewskaja (11); see also the method of Plugge (12), described under separation of papaverine.)

Narcotine crystallizes from alcohol in colorless prisms of m. p. 176° (8) (13). It may be sublimed (14) (15) (*cf.* Blyth (16)), and has been detected in smoke from the opium pipe (17). The alkaloid is insoluble in cold water, but slightly soluble in hot, from which it separates crystalline on cooling. At 20°, 100 c. c. of saturated solution contains narcotine in grams as follows: Acetone, 4.9; benzene, 3.4; toluene, 2.2; ether, 0.4; chloroform, 45.9; absol. alcohol, 0.40; water, 0.03 (at 30°); petroleum ether (b. p. 82°), 0.02. Other solubilities are given in the original (18). Narcotine is slightly soluble in ammonia, but not in cold alkalies; in hot alkali it dissolves with formation of the alkali salt (8) (15) (20). Long-continued boiling with excess alkali splits it to hydrocotarnine and opianic acid (8).

Narcotine is a weak base (21) (22), without effect on litmus (12) (23) (24); it may be extracted with organic solvents from even strongly acid solutions (12). Dissociation constant, Kolthoff (25), Arnall (26). In titrations involving narcotine (27), an indicator of the range of bromphenol blue should be used (22). Electrometric titration (28) (29); exhaustive references on titration are given by Müller (30).

Narcotine is levorotatory; in chloroform solution $[\alpha]_D = -199.85°$ (31) (*cf.* Hesse (32)), $[\alpha]_D^{33} = -198.0°$; in toluene, $[\alpha]_D^{32} = -148.75°$ (33); in benzene solution, $[\alpha]_D = -229°$ (34). *d*-Narcotine, obtained by resolution of gnoscopine, is identical with natural narcotine, but exhibits the opposite rotation, $[\alpha]_D = +199.92°$ (31). Mixing the optical antipodes yields gnoscopine, which is likewise formed by racemization of natural narcotine under various conditions (see Gnoscopine). Solutions of *l*-narcotine in acid are dextrorotatory (35): Hydrochloric acid $[\alpha]_r = +47°$ (32); sulphuric acid $[\alpha]_D^{32} = +57.25°$, $[\alpha]_D^{29} = +50.0°$ (33); acetic acid $[\alpha]_D^{16} = +52.17°$ (36); oxalic acid $[\alpha]_D = +62°$ (34).

Gaubert (37) claimed that narcotine may exist in a β-form (above 80°) and a γ-form (50° to 80°); Kremann and Schniderschitz (38) could find no evidence for this in the cooling curves.

Narcotine crystals have the refractive indices 1.525 and 1.69 (6); density 1.39 (39).

The absorption spectrum has been determined (40) (41) (42) (43).

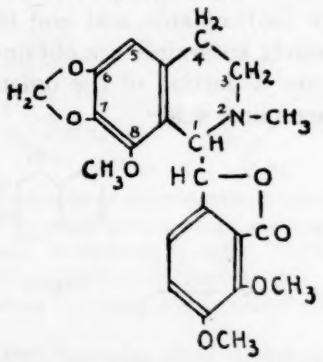
The heats of combustion and of neutralization are given by Leroy (23).

On the basis of early analyses (44) (45) the formula $C_{23}H_{25}O_7N$ was assigned to narcotine. Matthiessen and Foster (46) in 1863 proposed $C_{22}H_{23}O_7N$, which was soon confirmed by other investigators (8) (47) (48).

The base contains a methyl group on tertiary nitrogen, and three methoxyl groups (49) (50) (51). The latter may be successively split by heating with hydrochloric or hydriodic acid; methyl halide and the demethylated bases dimethylnornarcotine,[28] methylnornarcotine, and nornarcotine (53),[29] result. Nornarcotine is alkali-soluble, and takes up oxygen readily.

Narcotine contains no hydroxyl group, and is not affected by acetic anhydride (54) [30] or acetyl chloride (56).

As a result of the work of Roser, Vongerichten, and others, the following structure has been accepted for narcotine, and has recently received confirmation through synthesis:



The structure differs from that of the alkaloid hydrastine (from *Hydrastis canadensis*) only by the presence of the methoxyl group in the 8-position.

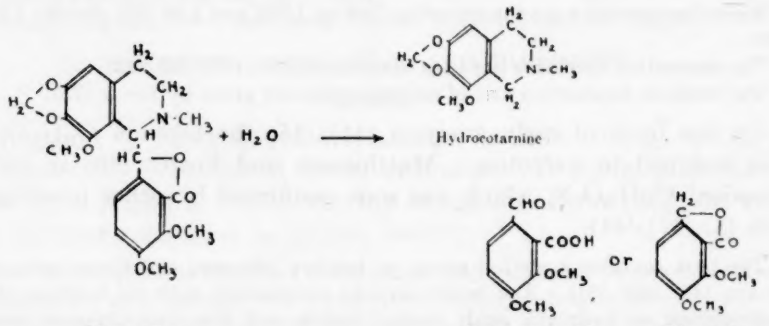
The first evidence concerning the narcotine nucleus was gained from its hydrolytic and oxidative decomposition. Heated with water to 140° (57) (58) or boiled with barium hydroxide (8) (*cf.* Beckett and Wright (57)) or sulphuric acid (57) the molecule splits with addition of the elements of water, to form the nitrogen-free meconin and the base hydrocotarnine, an alkaloid already isolated from opium. The primary products of the reaction are probably hydrocotarnine

[28] Formed also by the action of 50% H_2SO_4 on narcotine (Armstrong (52)).

[29] The prefix "nor" refers to the normal or parent compound; it is somewhat loosely used, and frequently indicates demethylation of the methylimido group as well.

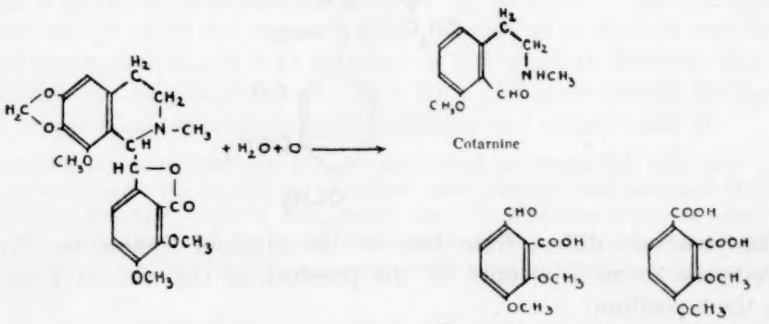
[30] With sulphuric acid and acetic anhydride it forms narcotine sulphonic acid or an acetylnarcotine, according to the conditions (Knoll and Co. (55)).

and opianic acid; the latter is then reduced to meconin by a partial decomposition of hydrocotarnine (57).[31, 32]



Narcotine Opianic Acid Meconin

Prolonged treatment of narcotine with reducing agents, as zinc and hydrochloric acid, breaks the molecule in a similar way directly to hydrocotarnine and meconin (57). When the hydrolysis is accomplished in the presence of oxidizing agents, as manganese dioxide and dilute sulphuric acid (19) (46) (57), chloroplatinic acid (44), ferric chloride (59), dilute nitric acid (7) (58) (60), chromic acid (56), or barium permanganate (56), opianic acid and the oxidation product of hydrocotarnine, namely cotarnine, are obtained.[33, 34] Under these experimental conditions, a portion of the opianic acid is often oxidized to the dibasic hemipinic acid.



Narcotine Opianic Acid Hemipinic Acid

By the action of hydrogen peroxide, narcotine is converted to an amine-oxide, without fission of the molecule; narcotine oxide is weakly basic and dextrorotatory (62).

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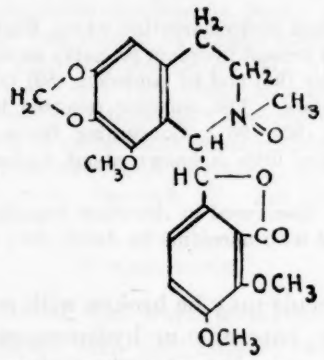
[31] Matthiessen and Wright (59), who first investigated the hydrolysis, believeder roneously that the products were meconin and cotarnine (at that time hydrocotarnine was not known).

[32] It has also been observed that narcotine on long boiling with 50% alcohol (58) or dilute acetic acid (63), gives in addition to gnoscopine and nornarceine, meconin and cotarnine.

[33] Further description of the methods of oxidation employed is given in the section devoted to cotarnine.

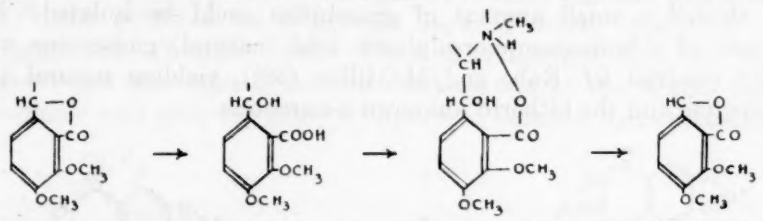
[34] Hydrastine, laudanosine, and benzoyltetrahydropapaverine likewise oxidize with manganese dioxide and sulphuric acid to give cotarnine types. From a comparative study of 1-substituted hydrocotarnines Pyman (61) finds that the presence of the benzyl (or substituted benzyl) group in this position is essential for the cleavage.



Narcotine Oxide

Refluxing narcotine with sodium or potassium in benzene results in replacement of two hydrogen atoms by metal (64).

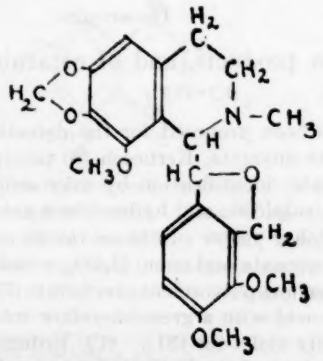
The solubility of narcotine in hot alkali (19) (32) is due to the opening of the lactone ring, with formation of an alkali salt, which may be isolated in a crystalline condition (20). A solution of the sodium salt precipitates narcotine slowly, more rapidly in the presence of mineral acids. This is taken as evidence of the existence of a hydroxy acid (or its inner salt) which slowly loses water to form narcotine; in the case of *d,l*-narcotine (gnoscopine) this inner salt can be isolated (20).



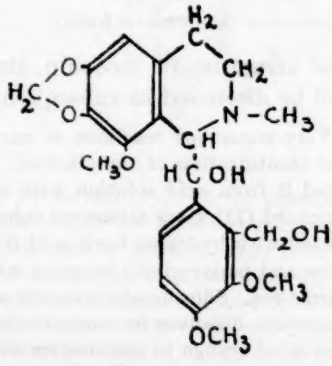
When narcotine methochloride or ethochloride is treated with alkali and steam (65) (66), the isoquinoline and lactone rings are opened, with formation of narceine and homonarceine, respectively (p. 82). The action of iodine in alcohol converts narcotine into tarconine methiodide (48) (67). (See Tarconine.)

Concerning condensations involving the 5-carbon atom of narcotine, see the section on isonarcotine.

Electrolytic reduction of narcotine gives dihydronarcotine (99), or tetrahydronarcotine (100); these probably have the following structures:



Dihydronarcotine



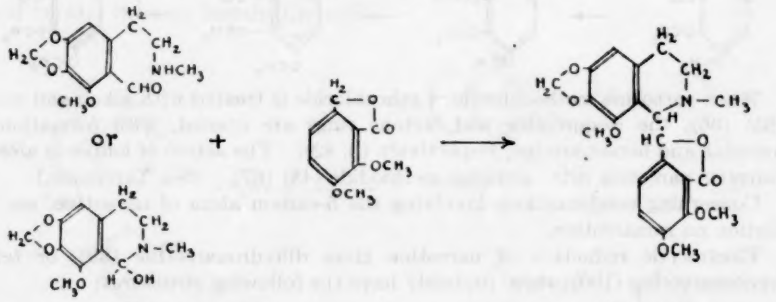
Tetrahydronarcotine

The methylnarcotine and propylnarcotine which Wertheim (92) and Hinterberger (93) believed to be present in opium probably do not exist; a careful search by Matthiessen and Foster (94) and by Anderson (50) failed to reveal them, nor have they been found since. The opianine reported by Hinterberger (93) is identical with narcotine (95) (96). Concerning Blyth's narcogenine (44) see Wertheim (92) (97). Very little is known about Anderson's teropiammon (7) (101).

The alkaloid aconella, discovered in *Aconitum napellus* by T. and H. Smith, was pronounced identical with narcotine by Jellet (98); only the physical properties were compared.

The narcotine molecule may be broken with comparative ease into a nitrogenous portion, cotarnine or hydrocotarnine, and a nitrogen-free portion, meconin, opianic acid, or hemipinic acid. The accepted formula for narcotine is based upon the structure of these fragments and the synthesis of narcotine from them.

The first synthetic attempts were made by Liebermann (68) (69) (*cf.* Wright (70)) and resulted in the formation of an isomer, isonarcotine. In 1911 Perkin and Robinson (31), after vain efforts to combine meconin and cotarnine in the presence of a variety of condensing agents, found that by simply boiling the two components in alcohol a small amount of gnoscopine could be isolated. By means of *d*-bromocamphorsulphonic acid (natural) gnoscopine was then resolved (*cf.* Rabe and McMillan (58)), yielding natural (*l*-) narcotine and the hitherto unknown *d*-narcotine.



Cotarnine (tautomeric form) Gnoscopine

The structure of meconin, its oxidation products, and of cotarnine will be discussed in subsequent sections.

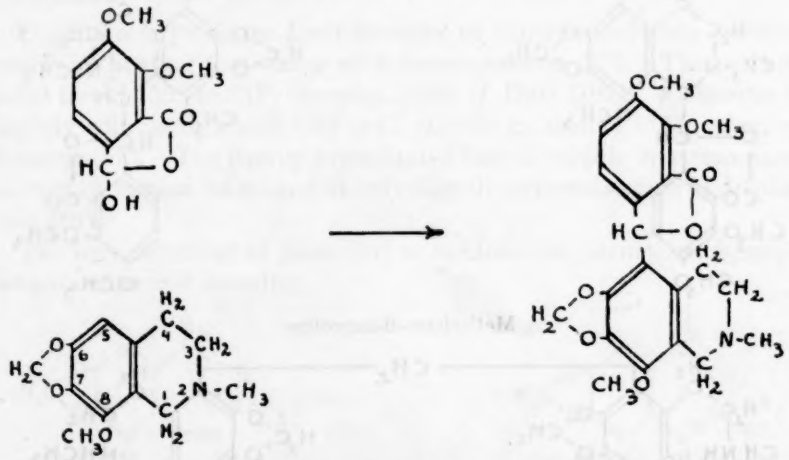
Very numerous reactions of narcotine have been proposed for the detection and identification of the alkaloid. For minute amounts, Kerbosch (6) precipitated it from acid solution with sodium acetate; identification by microscope. Reichard (71) gives numerous color tests with sulphuric and hydrochloric acids; heated with hydrated boric acid it forms a sulphur-yellow substance (as do narceine and papaverine); warming with sodium arsenate and conc. H_2SO_4, a stable purple-red. Silicoduodecitungstic acid gives a yellow, pulverulent precipitate (72). Narcotine dissolves in concentrated sulphuric acid with a greenish-yellow color, becoming orange to carmine on warming, finally violet (8) (31). (*Cf.* Erdmann (73), Husemann (74), How (119).) A modification of the Keller layer test using

basic magnesium hypochlorite is described by David (75). Precipitation as the chromate or dichromate was studied by Plugge (76); as the hydroferro- and hydroferri-cyanides, by Cumming and Brown (77). Narcotine picrate is described by Maplethorpe and Evers (78). Other color and precipitation reactions are described by Jörgensen (48) (Dragendorff's reagent), Scholtz (79) (o-xylylene bromide), Bruylants (80) (Fröhde-Buckingham reagent), Labat (81) (sulphuric acid and phenols), Scarpitti (120) (Piutti's reagent). The behavior of narcotine with 69 reagents is given by Kerbosch (6). For quantitative estimation of narcotine, see Annett (82).*

ISONARCOTINE

Liebermann (68) found that when a mixture of opianic acid and hydrocotarnine is treated with very cold 73 per cent sulphuric acid, condensation takes place. Treatment of the product with water and sodium carbonate, and recrystallization from alcohol, gives white needles of m. p. 194° (narcotine melts at 176°, gnoscopine at 232°). Isonarcotine dissolves in concentrated sulphuric acid with intense carmine color, in contrast to narcotine, which gives a greenish-yellow color. The same product is obtained by using fuming hydrochloric acid (sp. gr. 1.19) at 60° to 70° (83).

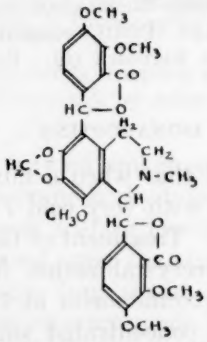
A structural formula for isonarcotine was first suggested by Freund (84)[35] and evidence for it brought forward shortly thereafter by Freund and Fleischer (86). These investigators believed that isonarcotine was formed through condensation of the lactone-form of opianic acid with the ana- (5-) hydrogen atom of hydrocotarnine:



This hydrogen in position 5 is distinguished by its activity. In the presence of sulphuric acid, it reacts readily with formaldehyde to give methylene-dihydrocotarnine (87). When, however, it is substituted by bromine, as in bromohydrocotarnine, condensation with formaldehyde or opianic acid no longer takes place. The reactive 5-hydrogen must still be present in narcotine, and it is in

[35] See also Perkin and Robinson (31), and Jones, Perkin, and Robinson (85).
* See Appendix, p. 357.

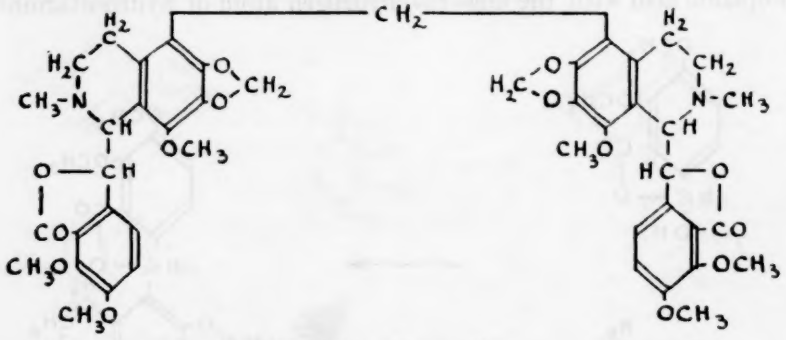
fact possible to condense narcotine with opianic acid (86). By this synthesis, a new asymmetric carbon atom is generated in a molecule already containing two, which leads to the formation of two stereoisomeric bases, α- and β-opian-lactyl-narcotine. Isonarcotine, not having the active 5-hydrogen, does not react with opianic acid.



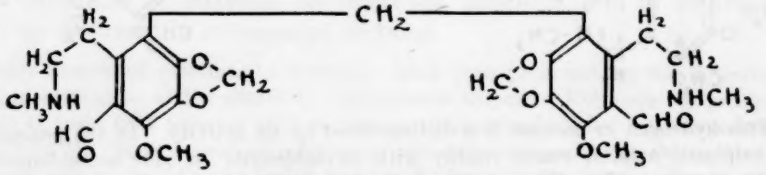
Opian-lactyl-narcotine

α-Opian-lactyl-narcotine methiodide, on treatment with silver oxide and strong alkali, undergoes a reaction parallel to the formation of narceine from narcotine methochloride, yielding α-5-opian-lactyl-hydrate-narceine (86).

Narcotine, like hydrocotarnine, condenses with formaldehyde, giving methylene-di-narcotine, which on oxidation behaves like narcotine, splitting off the opianyl groups with formation of methylene-di-cotarnine. Isonarcotine, as would be predicted, does not react with formaldehyde (86).



Methylene-di-narcotine



Methylene-di-cotarnine

Attempts to resolve isonarcotine through the *d*- and *l*-acid tartrates resulted only in optically inactive material (88).

Isonarcotine ethohydroxide does not undergo the ring scission which would be expected to give compounds of the narceine type (88).

Cotarnine

Cotarnine was first prepared by Wöhler (19) in 1844, by oxidation of narcotine with manganese dioxide and sulphuric acid; in the same year, Blyth (44) found it among the products from the decomposition of narcotine platinichloride in boiling water.

The hydrate formula $C_{12}H_{13}O_3N + H_2O$ (46) (57) (59) (89) was assigned to cotarnine for many years. While the anhydrous base could not be isolated, nevertheless all cotarnine salts were found to be derived from $C_{12}H_{13}O_3N$. Roser (60), in 1888, showed the supposed crystal-water to be actually water of constitution, and the true formula to be therefore $C_{12}H_{15}O_4N$. Salt formation takes place with the closure of a new ring and elimination of water.

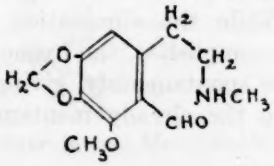
Beckett and Wright (57) prepared cotarnine by addition of 3 parts of 60 per cent manganese dioxide to a boiling solution of 2 parts narcotine in 33 parts of 10 per cent sulphuric acid. 100 g. narcotine yielded 20 to 25 g. of purified cotarnine.

Anderson's method (7) consists of warming 1 part of narcotine with 2.8 parts of nitric acid (sp. gr. 1.4) and 8 parts of water at 49° until no more solid separates. The flocculent material "teropiammon" is filtered out, and the cotarnine precipitated with concentrated potassium hydroxide. The yield is about 40 per cent of the weight of narcotine used (60).

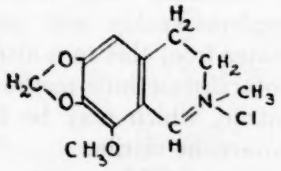
Cotarnine has also been obtained by oxidation of hydrocotarnine (57) (90), from heating gnoscopine with dilute acetic acid (63), from long boiling of narcotine with 50 per cent alcohol (58), from oxidation of oxynarcotine (91) or narcotine hydrochloride (59) with ferric chloride, or from heating narcotine alone to 200° (59). Sulphuric acid and narcotine heated to 280° F. in a sealed tube gave cotarnine sulphate and meconin (49).

Cotarnine crystallizes from benzene or ether in colorless needles, which on heating lose water with decomposition (57). The melting point lies at 132° to 133° (decomp.) (60) *cf.* Dott (102). Cotarnine is slightly soluble in water (19) (44), soluble in alcohol (19), ether, or benzene (57). The freshly precipitated base is soluble in ammonia or sodium carbonate solution, but only slightly so in potassium hydroxide (44) (59).[36]

The investigations of Roser led to the following structural formula for cotarnine and its salts:



Cotarnine

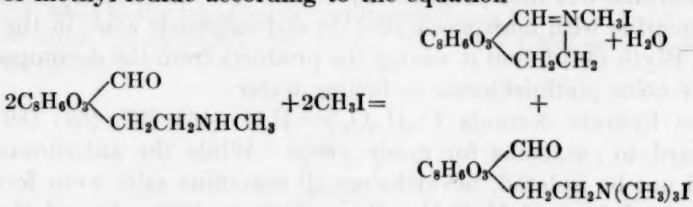


Cotarnine Chloride

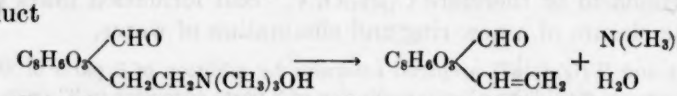
The presence of one methoxyl group in the base is shown by its behavior with hydriodic or hydrochloric acid. Heated with the latter to 140°, it splits out methyl chloride, giving the hydrochloride of cotarnamic acid, $C_{11}H_{13}O_4N$ (46) (59) (103) or $C_{11}H_{11}O_3N \cdot H_2O$ (104).

[36] *Cf.* Liebermann, Ber. 37, 211, note 2 (1904).

Cotarnine behaves as a secondary amine; it reacts with two molecules of methyl iodide according to the equation



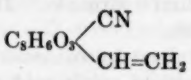
Following the usual course of exhaustive methylation, cotarninemethine methiodide decomposes further with alkali to a nitrogen-free product



Cotarninemethine methohydroxide — Cotarnone

which still contains the methoxyl group and is an aldehyde (oxime formation) (60) and takes up bromine readily.

In the case of the closely related cotarnone nitrile (105)

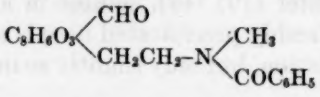


the dibromide can be isolated. The structure of cotarnone and its transformation to gallic acid will be considered in a subsequent paragraph.

Cotarninemethine methochloride reacts with excess of bromine water to split out the aldehyde grouping as carbon dioxide, forming dibromocotarnine ethyltrimethylammonium bromide,

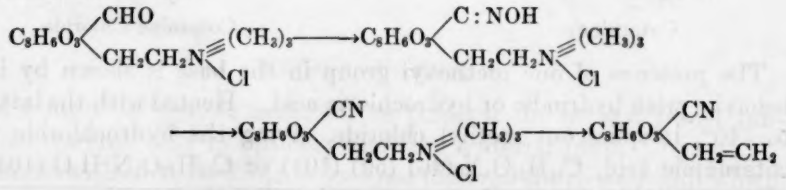
$$CH_2O_2{:}OCH_3{\cdot}C_6Br_2{\cdot}CH_2CH_2N(CH_3)_3Br \text{ (106)}.$$

The secondary nature of the cotarnine amino group is further shown by its ability to react with benzoyl chloride to yield benzoyl cotarnine

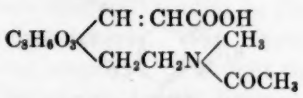


in which the aldehyde group may be demonstrated through oxime and phenylhydrazone formation (105).

Cotarnine itself yields an oxime, to which the isonitroso group confers weakly acid properties (105). While the elimination of water from this to a nitrile has not been accomplished, the oxime of cotarninemethine methochloridel oses water spontaneously, giving a nitrile, which may be further degraded to the already mentioned cotarnone nitrile:

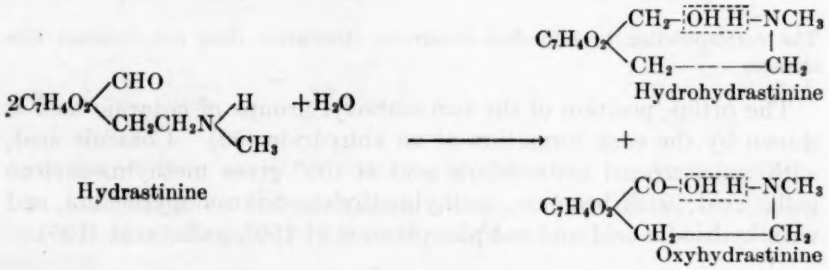


Cotarnine condenses readily with substances containing a methylene group. Bowman (89) carried out the first of these reactions, by refluxing cotarnine with acetic anhydride.[37] Acetylation of the amino group and a Perkin reaction take place, resulting in acetylhydrocotarnine acetic acid (60) (107), better named acetyl cotarnine acetic acid (108)



Condensation with acetone, malonic ester, acetoacetic ester, and a number of similar substances occurs with the greatest ease. The structure of these compounds will be considered with the question of tautomerism of cotarnine.

Strong support for Roser's conception of cotarnine as an aromatic aldehyde is to be found in the transformation of the closely related hydrastinine [38] by the action of alkali into hydrohydrastinine and oxyhydrastinine (109). This reaction runs like the conversion of benzaldehyde into benzyl alcohol and benzoic acid, and was formulated by Roser as (60):



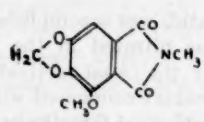
Hydrastinine

Hydrohydrastinine

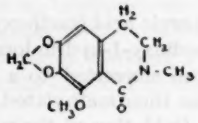
Oxyhydrastinine

In the case of cotarnine itself, only the reduction product, hydrocotarnine, can be isolated (105).

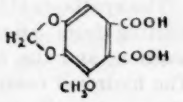
The first direct evidence [39] of the presence of an aromatic ring in cotarnine was obtained by oxidation. The action of potassium permanganate results in three products, cotarnic acid methylimide, oxycotarnine, and cotarnic acid (110). The last is likewise formed



Cotarnic Acid Methylimide



Oxycotarnine



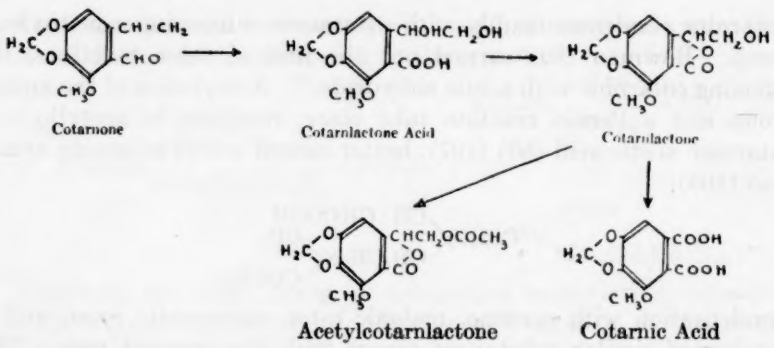
Cotarnic Acid

stepwise by the permanganate oxidation of cotarnone (60) (105), confirming the structure assigned to this substance.

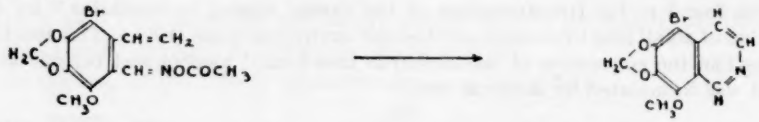
[37] Beckett and Wright (54) obtained cotarnine unchanged from treatment with acetic anhydride "under various conditions."

[38] Hydrastinine and cotarnine differ only in that the former contains no methoxyl group.

[39] *Cf.* Pelletier, Ann. chim. phys. (2) **50**, 252 (1832).

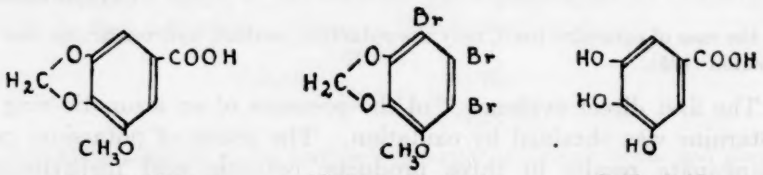


Cotarnone forms an oxime readily; in the case of bromocotarnone, the oxime occurs in two forms. The acetyl derivative of bromocotarnone-α-oxime loses acetic acid easily, being transformed to methoxymethylenedioxybromoisoquinoline (106).



The corresponding bromine-free cotarnone derivative does not undergo this change.

The ortho- position of the two carboxyl groups of cotarnic acid is shown by the easy formation of an anhydride (60). Cotarnic acid, with concentrated hydrochloric acid at 100° gives methylmethylene gallic acid; with bromine, methylmethylene-tribromopyrogallol, and with hydriodic acid and red phosphorous at 150°, gallic acid (105).



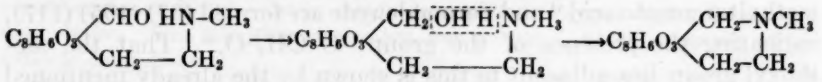
The synthesis (111) of cotarnic acid (methoxyhydrastic acid) was accomplished starting from 5,6-methylenedioxy-1-hydrindone, which was nitrated in the 7-position, and the nitro group converted to a hydroxyl by the usual method.[40] The hydroxyl compound was then methylated, and the product condensed with piperonal in dilute alkali. Oxidation of the resulting 7-methoxy-5,6-methylenedioxy-2-piperonylidene-1-hydrindone with permanganate gave cotarnic acid.

The action of reducing agents, as zinc and hydrochloric acid (57)[41] on cotarnine results in the formation of hydrocotarnine, a tetrahy-

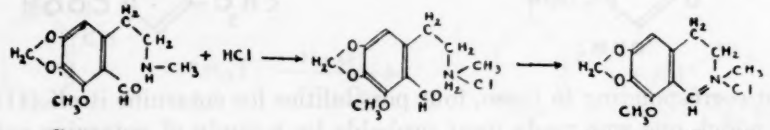
[40] The only evidence for assigning the hydroxyl (and therefore the nitro) group the 7-position is the intense violet coloration given with ferric chloride, which indicates that it is probably adjacent to the carbonyl group.

[41] Sodium amalgam and hydrochloric acid give a nearly quantitative reduction (113); electrolytic reduction, see Bandow and Wolffenstein (112).

droisoquinoline derivative. The relationship of this to cotarnine was was first expressed by Roser (60) in the formulas

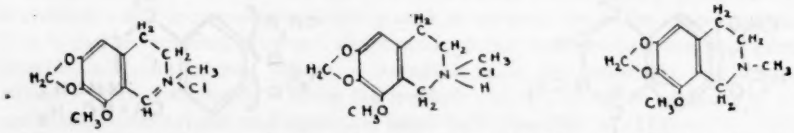


The formation of the salts of cotarnine takes place with loss of water and closure of a new ring (60) similar to the formation of quinoline from aminocinnamic aldehyde. The regeneration of cotarnine from these salts is without analogy. The fact that the salts of cotarnine are colored [42] may be adduced as additional evidence for Roser's salt formula.



Cotarnine Cotarnine Chloride

Reduction of cotarnine to hydrocotarnine in acid solution may then be considered as addition of hydrogen to the double bond:

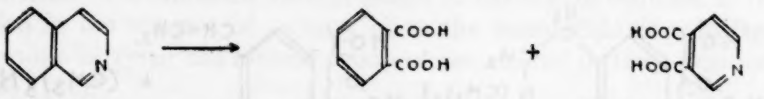


Cotarnine Chloride Hydrocotarnine Hydrochloride Hydrocotarnine

Further evidence for this salt formula is found in the oxidation of cotarnine salts to apophyllenic acid (7) (19) (114),[43] the methylbetaine of cinchomeronic acid (115).

Cinchomeronic Acid Apophyllenic Acid

This structure for apophyllenic acid has been confirmed by Roser's synthesis (116). The behavior of cotarnine on oxidation, on the one hand to cotarnic acid, on the other hand to apophyllenic acid, presents therefore a very close analogy to that of isoquinoline, which goes to phthalic acid and cinchomeronic acid.

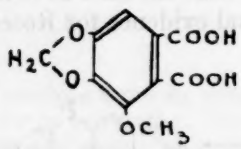


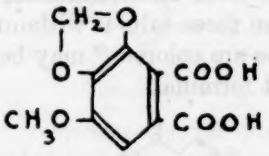
Isoquinoline Phthalic Acid Cinchomeronic Acid

The location of the methoxyl and methylenedioxyl groups in the aromatic nucleus of cotarnine was accomplished through the investi-

[42] Contrary to other observers, Bruns, Arch. Pharm. 243, 57 (1905) states that cotarnine iodide is colorless.
[43] Apophyllenic acid was so named by Wöhler from the similarity of its crystals to those of apophyllite.

gation of cotarnine anil and the tarconine compounds. When N-methyltarconium hydroxide is heated with barium hydroxide, methyltarconinic acid[44] and formaldehyde are formed (67) (105) (117), indicating the presence of the group $-O-CH_2-O$.[45] That the methoxyl group lies adjacent to this is shown by the already mentioned decomposition of cotarnic acid to gallic acid. There are, therefore, but two possibilities for cotarnic acid (105):





but corresponding to these, four possibilities for cotarnine itself (118) of which one was made most probable by a study of cotarnine-anil.

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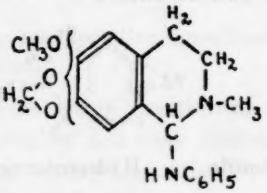

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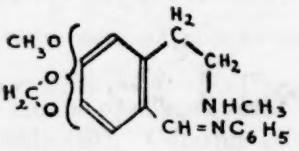

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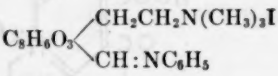

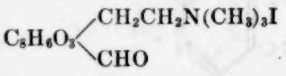

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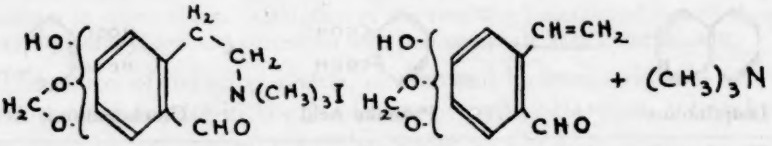

[44] The chemistry of the tarconine compounds will be considered in detail in a later paragraph.

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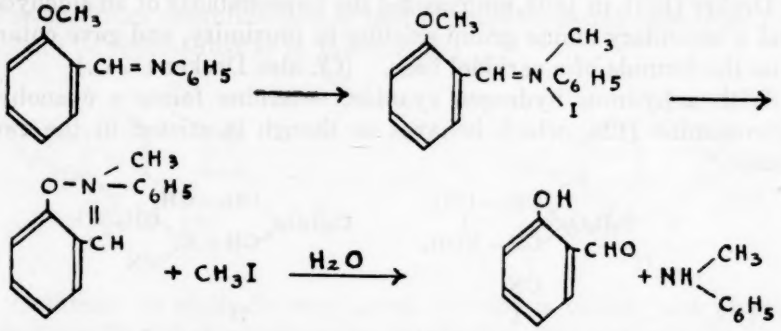
The product is a trihydroxy compound, cotarnoline, isolated in good yield as the sulphate (150).

This remarkable reaction was made more comprehensible by a study of the anils of the methoxybenzaldehydes, where it was found that only the anil of o-methoxybenzaldehyde lost a methyl group from oxygen during exhaustive methylation. The following mechanism was proposed, which is equally applicable to cotarnine-anil.



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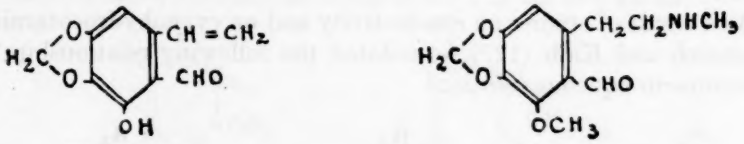
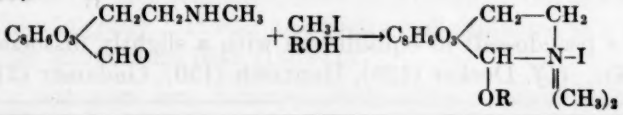
This peculiarity of o-methoxybenzaldehyde makes it exceedingly probable that in cotarnine and in norcotarnone the groups in question lie in the ortho-position. This is further confirmed by the violet color shown by norcotarnone with ferric chloride, and the intense yellow of its alkali salts, characteristic reactions of ortho-hydroxy compounds. Since the methylenedioxyl group is adjacent to the methoxyl, norcotarnone and cotarnine must be represented as (118):



Norcotarnone Cotarnine

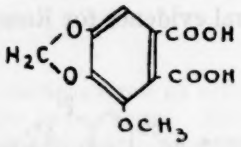
TAUTOMERISM OF COTARNINE

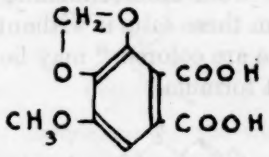
At the time the amino-aldehyde and dihydroisoquinoline formulas for cotarnine and its salts, respectively, were proposed, Roser [46] recognized certain facts which were difficult of explanation. Among these were (*a*) the precipitation of cotarnine in the aldehyde form from its salts, (*b*) the oxidation of hydrocotarnine (a tetrahydroisoquinoline derivative) to cotarnine, and (*c*) the derivation of the tarconines from cotarnine. Furthermore, methyl iodide in alcohol, in contrast to its action in the absence of solvent, gives the methiodide of a hydrocotarnine carrying the alkoxyl group of the alcohol in the 1-position (105) (121).



[46] Roser, Ann. **249**, 170 (1888).

gation of cotarnine anil and the tarconine compounds. When N-methyltarconium hydroxide is heated with barium hydroxide, methyltarconinic acid[44] and formaldehyde are formed (67) (105) (117), indicating the presence of the group $-O-CH_2-O$.[45] That the methoxyl group lies adjacent to this is shown by the already mentioned decomposition of cotarnic acid to gallic acid. There are, therefore, but two possibilities for cotarnic acid (105):





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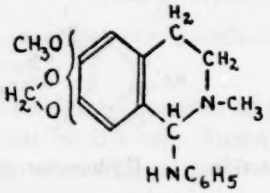

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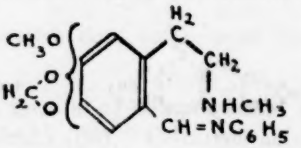

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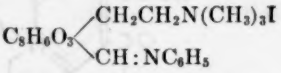

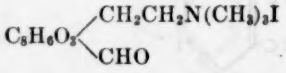

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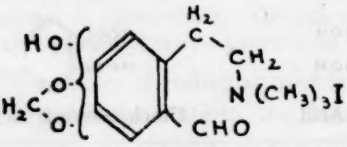

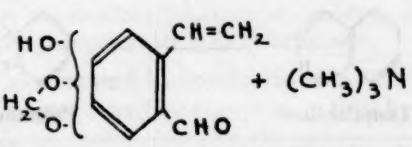

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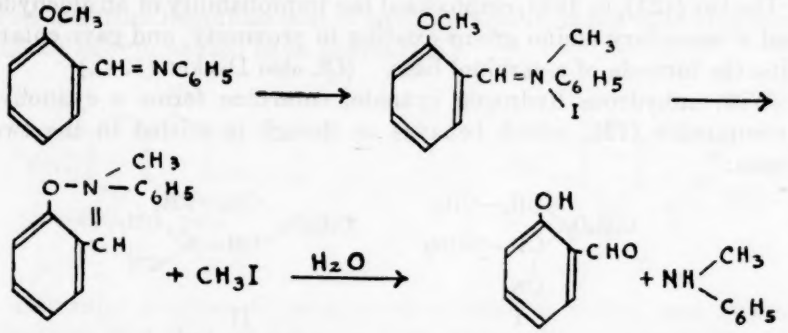

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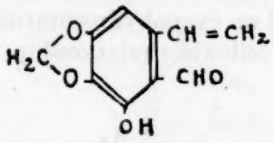
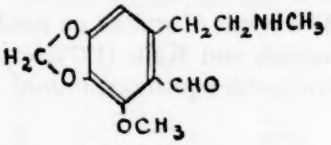


Norcotarnone



Cotarnine

TAUTOMERISM OF COTARNINE

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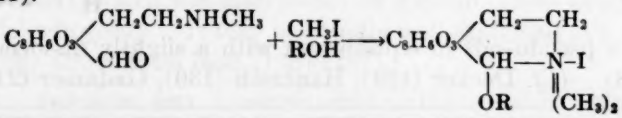
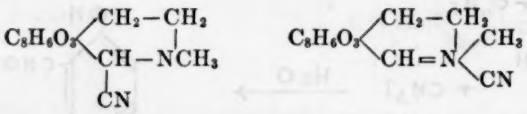


[46] Roser, Ann. 249, 170 (1888).

Freund (122) found that cotarnine and alcohol alone yielded an ethoxy compound in which the ethoxyl group did not split out on boiling with HCl, but on the other hand was immediately removed (with formation of cotarnine) by treatment with cold water.

Decker (123), in 1893, emphasized the improbability of an aldehyde and a secondary amino group existing in proximity, and gave cotarnine the formula of a carbinol base. (*Cf.* also Decker (124).)

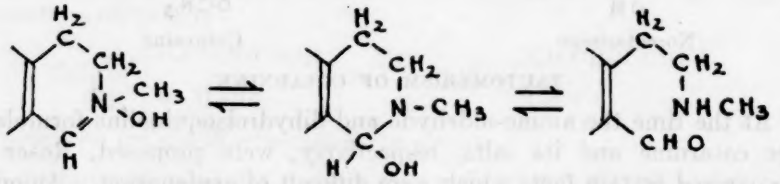
With anhydrous hydrogen cyanide, cotarnine forms a cyanohydrocotarnine (125) which behaves as though it existed in the two forms:[47]



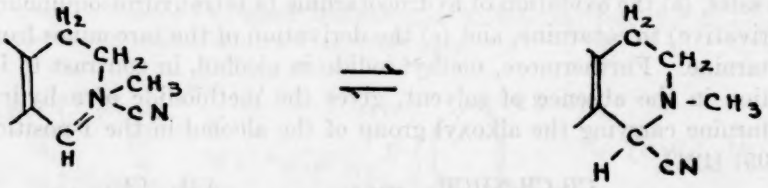
I II

The stability of cyanohydrocotarnine to alkali and formation of a methiodide point to Formula I; on the other hand its reaction with silver nitrate and its formation from cotarnine chloride and potassium cyanide (127) make Formula II probable (125). With hydrogen sulphide, cotarnine yields a sulphide which behaves as a tautomeric mixture; cotarnine peroxide, from the action of hydrogen peroxide, however, behaves only as though oxygen were attached to carbon (125).

As a result of studies on conductivity and on cyanohydrocotarnine, Hantzsch and Kalb (127) formulated the following relationship for cotarnine in aqueous solution:



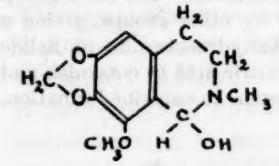
and for cyanohydrocotarnine,



that is, a pseudo-salt in equilibrium with a slightly dissociated true salt (128). (*Cf.* Decker (129), Hantzsch (130), Gadamer (218).)

[47] Spectral evidence (126) shows only the carbinol form present, though this is doubtless easily transformed to the ammonium form.

Examination of the spectra of solutions of cotarnine and its derivatives has thrown much light on these complicated relationships (126) (131). Cotarnine in ether or chloroform solution is colorless and apparently in the same structural condition as in the solid state. The spectrum resembles that of hydrocotarnine, hence solid cotarnine should be represented as in Formula I.



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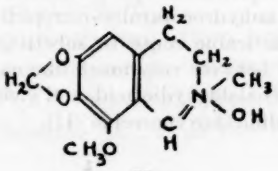
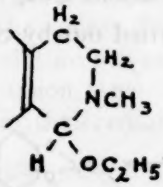
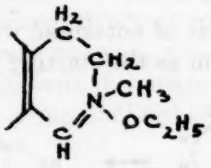


II

Cotarnine in alcoholic or aqueous solution is yellow, and gives a spectrum like that of cotarnine chloride, or like cotarnine freshly liberated from its salts by silver oxide; therefore in these solvents it exists as the ammonium base, Formula II. When an alcoholic solution of cotarnine is diluted, the extent to which the spectrum is transmitted diminishes, and the position of the absorption bands is altered. These observations force the conclusion that the alcohol brings about a constitutional change, which is confirmed by the chemical behavior of ethoxyhydrocotarnine (from the action of alcohol on cotarnine, Freund); it seems to exist in the two forms:





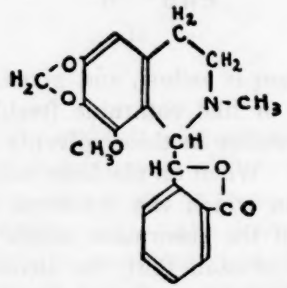
The lack of color of the solid favors Formula I which is supported by its spectrum in ethereal solutions. The alcoholic solution of ethoxyhydrocotarnine becomes rapidly colored, and gives spectra closely approaching those of cotarnine chloride; hence, when cotarnine is dissolved in alcohol, it passes slowly from the carbinol form into the ammonium form. Alkalies favor the reverse change (131). No evidence is found in the spectra for the existence of more than two forms of cotarnine.

The reaction of cotarnine or its salts with the Grignard reagent (132) (133) (134) (135) results in 1-substituted hydrocotarnines (under certain conditions also a dimolecular reduction product, α-di-hydrocotarnine (134)) which was interpreted by Freund (1906) as a reaction of the aldehyde group. It may be equally well explained as a reaction of the cyclic ammonium base (136) (137).

Cotarnine undergoes very numerous condensation reactions with methyl ketones (107) (138) (139), phenols (140), acetoacetic esters (138), phthalide (141), nitrotoluenes, nitromethane (137), amides, imides (137) (142), nitrohomo-

veratrol and nitrohomopiperonyl alcohol (143), etc. It has been difficult in many cases to show whether these products are derivatives of the imino-aldehyde form, or of the tetrahydroisoquinoline form. Cotarnine probably condenses as pseudo-base (carbinol base) or imino-aldehyde, according to the nature of the reagent employed (138) (140). Robinson believes that evidence for the existence of the latter form is entirely lacking (137).

Of particular interest is the condensation of cotarnine with phthalide and nitrophthalide (141), which leads to narcotinelike substances. The nitro group in anhydrocotarnine-nitrophthalide may be replaced by other groups, giving a practicable route to substituted narcotine types. Anhydrocotarnine-phthalide (I) behaves very much like narcotine, oxidizing with nitric acid to cotarnine and phthalaldehydic acid, and yielding by a reaction analogous to narceine formation, dedimethoxynarceine (II).



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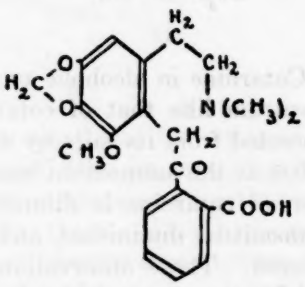
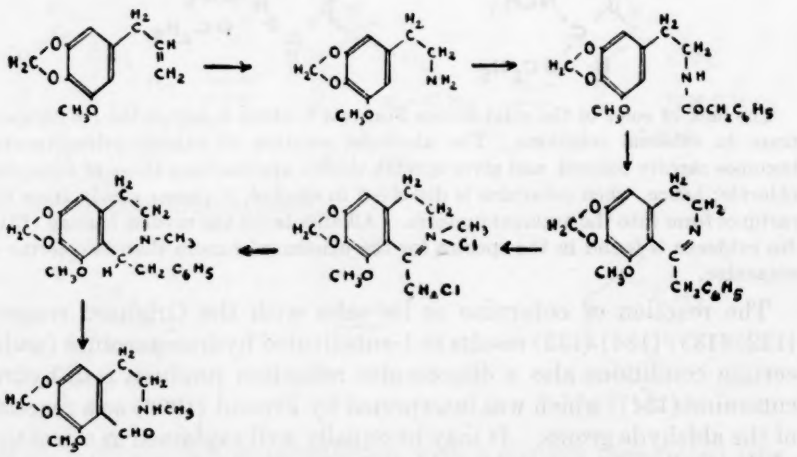


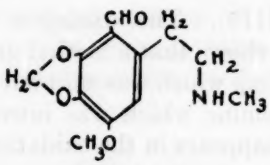
II

Condensation of cotarnine with 6-nitrohomoveratrol and subsequent elimination of the nitro group gives a new alkaloid of the laudanosine group (143).

The synthesis of cotarnine was first carried out by Salway (144), using myristicin as the starting point.



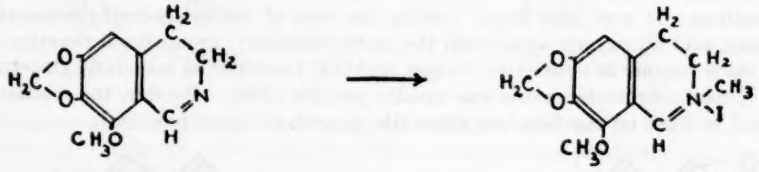
The formation of the dihydroisoquinoline ring from the phenacetyl derivative takes place with both ortho carbon atoms, so that in addition to cotarnine, an isomer, neo-cotarnine is obtained:



Neo-cotarnine

This synthesis does not constitute a proof of structure.

A modification (145)[48] of the Salway synthesis leads from homomyristicyl aldehyde through the oxime, amine, amine formate to homomyristicyl formamide, which with $POCl_3$ closes a dihydroisoquinoline ring to norcotarnine. The methiodide of this is identical with cotarnine iodide:



Norcotarnine Cotarnine Iodide

The Tarconines

The series of compounds classified as tarconines is of importance primarily because of its bearing on the structure of cotarnine. The relationship between the various members is complicated, and many compounds have been described of whose structure nothing is known. The nomenclature has undergone some changes, and for the purpose of this discussion tarconine will represent the unknown parent substance, 6,7-methylenedioxy-8-hydroxyisoquinoline betaine (106) (146).

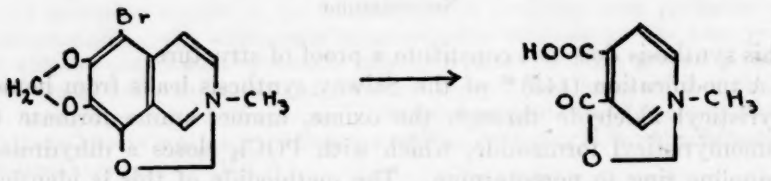
I. Tarconine II. N-Methyltarconine ("Tarconine")

Tarconine derivatives were first prepared and named by Jörgensen (48) (147) in 1869–70; the base N-methyltarconine was made by Wright (70) in 1877 and named by him "tarconine."

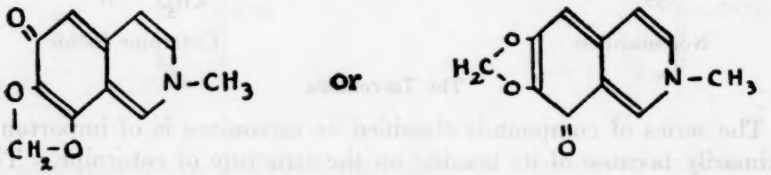
When cotarnine chloride is treated with excess of bromine water, a yellow precipitate of bromocotarnine superbromide is formed. The cotarnine grouping in this is still essentially intact, since removal of excess bromine with reducing agents yields bromocotarnine. If the superbromide is heated to 190° to 200°, it suffers loss of hydrobromic acid and methyl bromide, with formation of the colored N-methyl-

[48] *Cf.* also Decker, D. R-P. 245095.

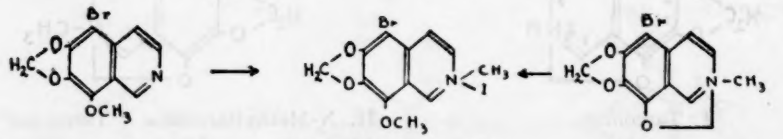
bromotarconine (70) (115). The oxidation of this substance to apophyllenic acid (115) shows that a methyl group is still attached to nitrogen; the methyl group which was split out was therefore removed from oxygen. The bromine which was introduced must be in the benzene ring since it disappears in the oxidation.



To account for these facts, Roser (105) suggested a p-quinoid structure for the tarconines, all of which are colored. This fixed the methoxyl of cotarnine in the 6-position. It was later found that in the case of methyl-N-methylbromotarconinic acid an oxygen atom from the methylenedioxyl group could function in the same manner as a tarconine former, and that therefore an o-quinoid structure for N-methylbromotarconine was equally possible (108). By this, the methoxyl would be fixed on the 8-carbon atom (its present accepted position).



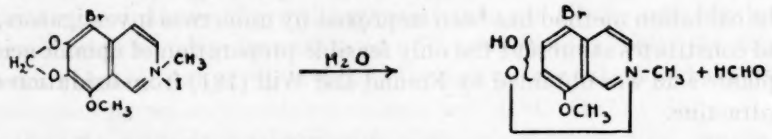
The quinoid hypothesis, however, was not tenable, since it was found (106) that the methyl iodide addition products from "bromotarconine" (N-methylbromotarconine) and from methoxymethylenedioxybromoisoquinoline, are identical. "Bromotarconine" must therefore possess an inner salt structure, like that of the hydroxyisoquinoline alkyl ammonium hydroxides of Claus (146).



Methoxymethylenedioxybromoisoquinoline | Methyl-N-methylbromotarconium Iodide | N-Methylbromotarconine

The action of ethyl iodide on N-methylbromotarconine results similarly in ethyl-N-methylbromotarconium iodide, in which the ethyl group is attached to oxygen (117). The ethyl and methyl iodide derivatives, on treatment with silver oxide form quaternary ammonium hydroxides (117) (147), which on boiling with barium hydroxide (67) (105) (117), lose the methylenedioxyl group as formaldehyde, giving, respectively, ethyl-N-methylbromotarconinic acid and methyl-N-methylbromotarconinic acid. In these compounds a

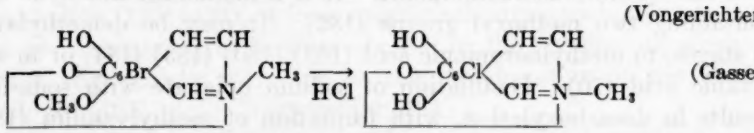
betaine linkage has been set up with one of the hydroxyls from the methylenedioxyl group. The reaction takes place with tarconium salts, but not with N-methyltarconine itself (117).



Through heating in hydrochloric acid, both of these tarconinic acids lose the alkyl group to form the same product, tarconic acid (Vongerichten (117)), or methylchlorotarconol (Gasser (108))—

$$C_{11}H_{10}BrO_3N + 2HCl = HBr + CH_3Cl + C_{10}H_7O_3N \cdot HCl$$

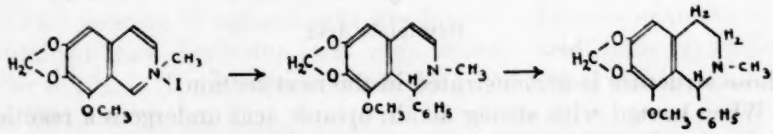
(Vongerichten)



(Gasser)

N-methylbromotarconine undergoes, furthermore, several little-investigated reactions. Oxidation with bromine gives cuprin, dibromapophyllin and bromapophyllenic acid (115). By the action of hot water it forms tarnine and cupronine. Hydrochloric acid acts on it at 130° to give nartinic acid (104) (117) (earlier named "nartine").

The reactions of N-methyltarconine, which is formed by heating bromocotarnine bromide (70) or by loss of methyl chloride from methyl-N-methyltarconium chloride (67), are very similar to those of N-methylbromotarconine. The relationship of methyl-N-methyltarconium iodide "tarconine methiodide" to cotarnine and hydrocotarnine is evident from the products obtained through reduction. With zinc and sulphuric acid hydrocotarnine is formed (90). Treatment with phenylmagnesium bromide gives methyl-N-methyl-1-phenyl-hydrotarconine [49] which reduces readily to 1-phenylhydrocotarnine (135) (148):



Iodotarconines, similar in every way to the bromotarconines, result from the action of iodine on narcotine (67) (90). Opianic acid and methyl-N-methyltarconium superiodide "tarconine triiodide" are the primary products. With reducing agents the latter gives on the one hand methyl-N-methyltarconium iodide, on the other hand methyl-N-methyliodotarconium iodide.

N-ethylbromotarconine as well as its methyl- and ethyl-tarconium derivatives are known, and have been converted to the corresponding tarconinic acids (106) (149).

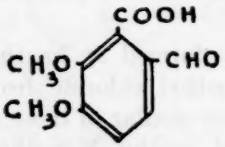
[49] An attempt to prepare the corresponding benzyl compound showed it to be much more unstable than the phenyl derivative (148).

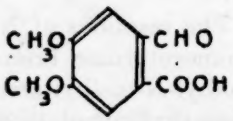
OPIANIC ACID

The appearance of opianic acid as the nitrogen-free oxidation product from narcotine was first mentioned by Liebig and Wöhler (178). The oxidation method has been improved by numerous investigators,[80] and constitutes at present the only feasible preparation of opianic acid. Opianic acid was obtained by Freund and Will (181) from oxidation of hydrastine.

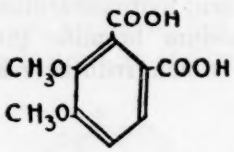
Opianic acid crystallizes in very fine prisms melting at 150°; it is soluble in 60 parts of hot water or 400 parts of cold water, soluble in alcohol or ether.

Opianic acid is of interest in the present discussion because of its bearing on the structure of narcotine, and it will therefore be considered chiefly from this standpoint. It is a monobasic aldehyde acid containing two methoxyl groups (182). It may be demethylated, in stages, to methylnoropianic acid (103) (180) (183) (184) or to noropianic acid (70). Distillation of sodium opianate with soda-lime results in decarboxylation, with formation of methylvanillin (185), whereby the positions of the methoxyl groups relative to aldehyde is revealed. On the basis of this, the structure of opianic acid is limited to two possibilities:





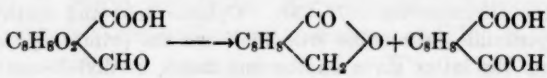
of which the second is eliminated by the oxidation of opianic acid to hemipinic acid (7) (19):



Hemipinic Acid

whose structure is demonstrated in the next section.

When heated with strong alkali, opianic acid undergoes a reaction of the Cannizarro type, giving meconin and hemipinic acid (94) (103).



Opianic acid is also converted to meconin by the action of reducing agents, as sodium amalgam or zinc and acid (46) (103). Meconin,

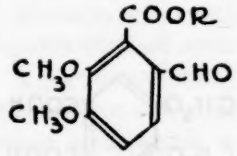
[80] Preparation of opianic acid from narcotine, see Wöhler (19), (MnO_2), Anderson (7), (HNO_3), Blyth (44), (H_2PtCl_6); most practicable method, Wegscheider (179); purification of opianic acid, Prinz (180).

opianic acid, and hemipinic acid are related as lactone, aldehyde, and acid.

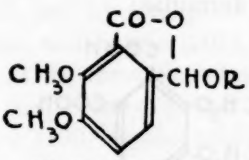
In the earliest investigations, Wöhler observed a transformation of opianic acid above the melting point into an alkali-insoluble form which he believed to be an isomer. This was undoubtedly the dimolecular opianic anhydride which is formed by the action of heat or of phosphorous pentachloride on opianic acid (186) (187) (188).

Opianic acid, in analogy with o-phthalaldehydic acid, reacts in two tautomeric forms as was early suspected by Liebermann (189) (190) (191) (192). It forms two series of esters, derived respectively from the normal aldehyde acid and from the hydroxyphthalide form. The normal or α-esters result from the action of silver opianate with alkyl iodide (179) (193), or from opianic anhydride with alcohols (194) and are constituted as in Formula I. In the presence of alcoholic potash they slowly rearrange to the pseudo-esters of the alcohol employed (195). (*Cf.* Wegscheider (194).)

The pseudo-esters [51] (Formula II) are formed when opianic acid or its chloride is heated with alcohols (193) (197) (198) and in contrast to the α-esters are readily hydrolyzed by boiling water.*



I. α-Esters

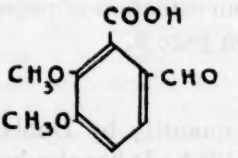


II. Pseudo-Esters

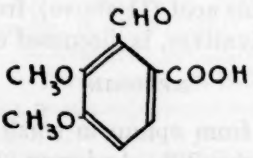
Opianic acid condenses in the pseudo-form with phenols or their methyl ethers in the p-position if this is unoccupied (195) (199) (200). The formation of iso-narcotine (p. 47) from opianic acid and hydrocotarnine involves this type of condensation.

Opianic acid was synthesized by Edwards, Perkins, and Stoyle (201) by oxidation of synthetic meconin (see below).

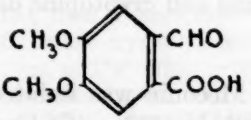
Two isomers of opianic acid are known. Pseudo-opianic acid is obtained from berberine, and meta-opianic acid from cryptopine. (See p. 101.) The latter was synthesized by Fargher and Perkin (202) in 1921.



Opianic Acid from Narcotine, m. p. 150°



Pseudo-opianic Acid from Berberine, m. p. 121°



Meta-opianic Acid from Cryptopine, m. p. 185°

[51] Concerning a more rational system of nomenclature, see Freund and Fleischer (196).

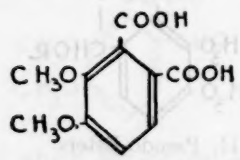
* See Appendix, p. 358.

HEMIPINIC ACID

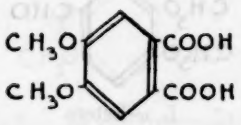
Hemipinic acid is formed when opianic acid is oxidized (19)[52] and hence in oxidations of narcotine (7) (19) (44) or of narceine (20). Its formation from opianic acid as the result of a Cannizarro reaction was mentioned above. It has also been observed as an oxidation product from berberine (204) (205) or corydalin (206).

Hemipinic acid usually crystallizes with two molecules of water, although samples containing ½ and 2½ molecules have been reported (179) (184). After drying at 100° it melts at 165° to 166° with foaming when heated slowly. The melting point is usually given as 180° (19) (203), but varies greatly with the method of heating, since the acid is partly converted to the anhydride even below the melting point (207).

Hemipinic acid will be considered here only in so far as it is concerned with the structure of opianic acid. It is a dimethoxyphthalic acid; on heating, it loses a molecule of water and is converted to the anhydride (185), a change which is also brought about by phosphorous pentachloride (180). In hemipinic acid the position of one carboxyl relative to the two methoxyl groups is certain from the relationship to opianic acid. Hemipinic acid must have one of the two formulas:



I



II

Wegscheider (179) (187) was able to prepare two monomethyl esters of hemipinic acid, thus showing Formula I to be correct. A compound having the structure II could yield but one monomethyl ester. The formula as established by Wegscheider was confirmed through the condensation of hemipinic anhydride with benzene to yield alizarin (203). Through the determination of the structure of hemipinic acid, the position of the carboxyl group in opianic acid was demonstrated.

The synthesis of hemipinic acid was accomplished by Edwards, Perkin, and Stoyle (201) by oxidation of synthetic meconin. The constitution of m-hemipinic acid (II above), from oxidation of papaverine and cryptopine derivatives, is discussed on page 6.

MECONIN

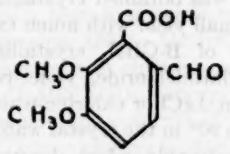
Meconin was isolated from opium in small quantity by Dublanc (208) in 1832. (*Cf.* Couerbe (209), Anderson (210).) It has also been obtained from the root of *Hydrastis canadensis* (211). It is formed during the oxidation of narcotine with nitric acid (7), by heating

[52] Preparation in quantitative yield from opianic acid, Lagodzinski (203).

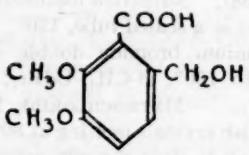
narcotine with dilute acetic acid (63), or when opianic acid or its chloride is reduced (46) (103) (180). Frerichs observed the formation of meconin when narcotine or hydrastine was heated to 200° with urea (212).

Meconin crystallizes from water in needles, and has the melting point 102° to 102.5°. It is soluble in 22 parts of boiling water, in 700 parts at 15.5°. It is optically inactive.

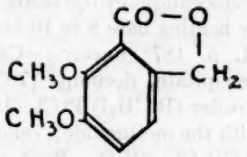
Its character as a lactone was first recognized by Wright (213).



Opianic Acid



Meconinic Acid



Meconin

Meconin dissolves in alkalies slowly with formation of meconinic acid, which is however stable only in the form of its salts (214). The condensation of meconin with cotarnine to gnoscopine (*d, l*-narcotine) has already been mentioned (p. 46).

Meconin was synthesized by Fritsch (215), and by a more advantageous method recently by Edwards, Perkin, and Stoyle (201).

A pseudomeconin, prepared by Salomon (216), through reduction of hemipinic anhydride, is also known. It is the lactone of pseudomeconinic acid, which was observed by Freund (100) in the oxidative degradation of tetrahydronarcotine (p. 45). Pseudomeconinic acid has also been obtained as the end product in hydrolytic degradation of berberal (217).

Descriptive Part (Narcotine, Cotarnine, and Tarconine)

NARCOTINE

NARCOTINE: B=$C_{22}H_{23}O_7N$. —HYDROCHLORIDE (151), crystallizes with varying amounts of water. B·HCl·$4H_2O$, B·HCl·$\frac{1}{2}H_2O$ (57), B·HCl·$3H_2O$ (23), B·HCl·H_2O (34). Very soluble in water often giving basic salts, as B_5·HCl, B_7·HCl, B_9·HCl (54); according to Leroy these basic salts form only on boiling the solution (23). —MERCURICHLORIDE, $(B\cdot HCl)_2HgCl_2$, small needles, diff. sol. in water or alcohol (152). —PLATINICHLORIDE, $(B\cdot HCl)_2PtCl_4+2H_2O$, amorphous yellow precipitate (8). —SULPHATE, $B_2\cdot H_2SO_4\cdot 4H_2O$, loses one H_2O at 100° (34). —SESQUISULPHATE, $B_4\cdot 3H_2SO_4\cdot 2H_2O$, from the base with 3 equivalents of dil. H_2SO_4 (153). —ACETATE, $B_3\cdot C_2H_4O_2\cdot H_2O$, from a large excess of acetic acid, needles (34). —DICHROMATE, $B_2\cdot H_2Cr_2O_7$ yellow crystals, decomp. 70° to 80° (8). —PICRATE, from alcohol-water (4 : 1,) m. p. 174° (78). —SILICODUODECITUNGSTATE, $B_4\cdot SiO_2\cdot 12WO_3\cdot 2H_2O$, yellow pulverulent comp., very insol. in water or alcohol (72). —CYANURATE, $B\cdot H_3C_3N_3O_3+1\frac{1}{2}H_2O$, m. p. 175° (154). —MECONATE, neutral salt, resinous, acid salt as needles (34). —BENZALSULPHITE, $B\cdot H_2SO_3\cdot C_6H_5CHO$, m. p. 70° (decomp.), from aqueous suspension of narcotine with SO_2 to solution, then benzaldehyde. In chloroform solution, the benzalanhydrosulphite, $B\cdot SO_2\cdot C_6H_5CHO$, decomp. 80°, is formed (155). —HY-

DROFERROCYANIDE, $B_2 \cdot H_4Fe(CN)_6 \cdot 2H_2O$, from acid or neutral solution, clusters of white crystals. The hydroferricyanide was too unstable for analysis (77). —TRIIODIDE, $B \cdot HI_3$, from B·HCl with I_2–KI. From alcohol, black rhombic plates, absorb polarized light, melt 109° to 120°. With SO_2 and NH_4OH, it yields narcotine, boiled with alcohol it gives tarconine triiodide and opianic acid (48). —MERCURINITRITE, $B_6 \cdot Hg(NO_2)_2$, from addition of narcotine in chloroform to aqueous $Hg(NO_2)_2$ (156). —ACID OXALATE, oil, very soluble in water (8). —ACID TARTRATE, amorphous, water-soluble (8).

NARCOTINE METHIODIDE: Viscous liquid, aqueous solution forms a double comp. with AgI (65). With silver bromocamphorsulphonate it gives narcotine-methyl-bromocamphorsulphonate (58). Narcotine methiodide was obtained crystalline by heating base 8 to 10 hours in a sealed tube, 150°. Small yield with much tar. M. p. 187° uncorr.; –Cadmium bromide double salt of $B \cdot CH_3I$, crystalline precipitate, decomp. 170° to 190°, $B \cdot CH_3I \cdot CdBr_2$; –Platinichloride, violet-red powder $(B \cdot CH_3I)_2PtCl_4$ (157). —METHOCHLORIDE, from AgCl or chlorine-water with the methiodide; yellowish crystals melting at 80° to 90° in the crystal water, $B \cdot CH_3Cl + 3H_2O$. With alkali it gives the oily methohydroxide, which decomp. with water to narceine; –Platinichloride, $(B \cdot CH_3Cl)_2PtCl_4 + H_2O$, m. p. 227° uncorr. (65) (66) (157).

NARCOTINE ETHIODIDE: $B \cdot C_2H_5I + H_2O$, from components in bomb tube 10 hours at 150°, yellow granular crystals from water, contain 1 H_2O; m. p. anhydrous 184°. Action of I_2 gives $B \cdot C_2H_5I \cdot I_2 + 1\frac{1}{2}H_2O$. The platinichloride, $(B \cdot C_2H_5I)_2PtCl_4 + 4H_2O$ melts anhydrous at 214° (157). (See also refs. 54 and 65.) —ETHOBROMIDE, $B \cdot C_2H_5Br + \frac{1}{2}H_2O$, in poor yield from sealed tube at 130° to 150° for 10 hours. M. p. anhydrous 204° (157). —ETHOCHLORIDE, from action of HCl on the ethobromide, isolated as salts; $(B \cdot C_2H_5Cl)_2ZnCl_2 + 3\frac{1}{2}H_2O$, m. p. 206°. $(B \cdot C_2H_5Cl)_2PtCl_4 + 3H_2O$, m. p. 178° (157). —ETHONITRATE, not crystalline (157).

NARCOTINE BENZOCHLORIDE: $B \cdot C_6H_5CH_2Cl + 3H_2O$, resinous. $B \cdot C_6H_5CH_2Cl \cdot CdBr_2 + \frac{1}{2}H_2O$ is a white crystalline powder, m. p. 146°; $(B \cdot C_6H_5CH_2Cl)_2PtCl_4 + 2H_2O$ yellow crystals, m. p. anhydrous 191° (157).

NARCOTINE-O-XYLYLENE BROMIDE: $B_2 \cdot C_6H_4(CH_2Br)_2$, needles from alcohol, m. p. 160° to 162° (79).

NARCOTINE-METHYL-BROMOCAMPHORSULPHONATE: $C_{33}H_{40}O_{11}NBrS$, from $B \cdot CH_3I$ with silver bromocamphorsulphonate, needles decomp. 231°. $[\alpha]_D^{23} = +101.0°$ in abs. alcohol (58).

NARCOTINE-METHYL-TRIIODIDE, (diiodonarcotine methiodide): $C_{22}H_{21}O_7NI_2 \cdot CH_3I$, from $B \cdot CH_3I$ with chlorine-water. Needles from alcohol, m. p. 149°. With excess of chlorine-water it gives methylnornarcotine-methyl-triiodide, m. p. 186° (66).

NARCOTINE SULPHONIC ACID: $C_{22}H_{23}O_{10}NS$, from B. in H_2SO_4 and acetic anhydride (55).

ACETYLNARCOTINE: $C_{24}H_{26}O_8N$, from B. digested at 80° with acetic anhydride-sulphuric acid compound. Crystals from alcohol, m. p. 159° to 161°, soluble in acids, insol. in alkali (158).

NARCOTINE MONOMERCURIACETATE: $C_{22}H_{22}O_7N \cdot HgOOCCH_3$, from oxidation of narcotine with mercuric acetate (36).

α-OPIANLACTYL-NARCOTINE: $C_{22}H_{22}O_7N \cdot C_{10}H_9O_4$, from condensation of narcotine and opianic acid in 73% H_2SO_4. M. p. 199°, in $CHCl_3$, $[\alpha]_D^{12} = -94.73°$. —PICRATE, 217°. —METHIODIDE, 210° to 230° (86). β-OPIANLACTYL-NARCOTINE, isomeric with the α-compound, m. p. 173° to 175°, in $CHCl_3$ $[\alpha]_D^{12} = -103.6°$. –Methiodide 200° to 222°. Yields an opianyl-narceine.

METHYLENE-DI-NARCOTINE: $C_{22}H_{22}O_7N–CH_2–C_{22}H_{22}O_7N$, from narcotine and formaldehyde in 80% H_2SO_4, m. p. 215° to 216°; in $CHCl_3$ $[\alpha]_D = -93.4°$. Oxidizes to methylene-di-cotarnine (86).

NARCOTINE OXIDE: $C_{22}H_{23}O_8N$, from slow oxidation of base with hydrogen peroxide; crystallizes from acetone, m. p. 229°; $[\alpha]_D = +139°$ in $CHCl_3$. —HYDROCHLORIDE, crystallizes from abs. alcohol, m. p. 191°; easily hydrolyzed to a hydroxy acid, $C_{22}H_{25}O_9N$, m. p. 212°, insol. organic media. Pb salt, Na salt; Sulphate, m. p. 148° (62).

NARCOTINE-SODIUM: $C_{22}H_{24}O_8NNa + 5H_2O$, from narcotine heated in normal NaOH with alcohol. Leaflets, m. p. 85° to 87°. Decomposes with water to narcotine (20).

DIMETHYLNORNARCOTINE: $C_{19}H_{14}O_4N(OCH_3)_2OH$, from the action of HCl (53) (177), or 50% H_2SO_4 (52), on narcotine. Amorphous; splits to methylnormeconin and cotarnine (59). METHYLNORNARCOTINE $C_{19}H_{14}O_4N(OCH_3)(OH)_2$, from long action of hot HCl on narcotine (53). Splits to normeconin and cotarnine (59); -Methyl triiodide, $C_{20}H_{21}I_2O_7N \cdot CH_3I$, from narcotine-methyl triiodide with chlorine-water. From alcohol, m. p. 186° (66). NORNARCOTINE: $C_{19}H_{14}O_4N(OH)_3$, amorphous, oxidized by air (53). Splits with water to normeconin and cotarnimide (59).

TETRAHYDRONARCOTINE: $C_{22}H_{27}O_7N$, from electrolytic reduction of narcotine; m. p. 128° from alcohol. —HYDROCHLORIDE, amorphous, decomp. 160° to 165°. —METHIODIDE, white needles from alcohol, decomp. 224°. Splits with KOH to pseudomeconinic acid and (2-methyl-3-methoxy-4, 5-methylenedioxyphenyl-6-ethyl) dimethylamine, an oil whose hydriodide ($C_{13}H_{19}O_3N \cdot HI + H_2O$) melts at 194°, and methiodide melts at 192° to 193°. Tetrahydronornarcotine contains two OH groups, and gives a dibenzoyl compound. $[C_{22}H_{25}(COC_6H_5)_2O_7N]_2H_2PtCl_6$ (100).

HYDRODESOXYNARCOTINE: $C_{22}H_{25}O_6N$, from electrolytic reduction of narcotine. Flat prisms from alcohol, m. p. 126°. Contains no OH group (99) (100).

ISONARCOTINE: ($B = C_{22}H_{23}O_7N$). —HYDROCHLORIDE, $B \cdot HCl + 2H_2O$, diff. sol. in cold water. —HYDROBROMIDE, and —HYDRIODIDE, crystalline, almost insol. cold water (68). —ACID *l*-TARTRATE, $B \cdot C_4H_6O_6 + 3\frac{1}{2}H_2O$, m. p. 180°. —METHIODIDE, white needles, m. p. 212°. —ETHIODIDE, m. p. 183°. Resolution of isonarcotine failed (88). BROMOISONARCOTINE, cryst. from dil. alcohol, m. p. 175°. NITROISONARCOTINE, cryst. from dil. alcohol, m. p. 205° (decomp.). METHYLNORISONARCOTINE, m. p. 209° (decomp.) (69).

COTARNINE

COTARNINE: ($B = C_{12}H_{13}O_3N$). —CHLORIDE (44), $(B \cdot HCl)_2 \cdot 5H_2O$ (159), yellow silky crystals, melting (anhydrous) at 192° (corr.) with decomp. (160). —AURICHLORIDE (44), $B \cdot HAuCl_4$, golden-yellow laminæ from hot alcohol, reddish-yellow broad needles from water, m. p. 136° to 137° (36) (144). —PLATINICHLORIDE, $(B \cdot HCl)_2PtCl_4$, long red prisms sparingly soluble in water (44) (57). —IODIDE, B·HI, yellow prisms from alcohol, sparingly soluble in acetone, water or alcohol, m. p. 184° to 186° (at 175° becomes violet) (60) (145). —TRIIODIDE (Hydriodide diiodide), $B \cdot HI_3$, from a dilute solution of cotarnine chloride, precipitated with alcoholic KI_3. Brown rhombic prisms from alcohol, m. p. 142°. Treated with sulphur dioxide and sodium carbonate it yields cotarnine again (48) (161). —PICRATE, yellow silky needles from hot water, sinters at 133°, melts at 143° (36) (144) (145). —PHTHALATE (neutral), from combination of the components in methyl alcohol or water; m. p. 102° to 105°; -Acid phthalate, yellow crystals m. p. about 115°; these phthalates are also advantageously prepared using phthalic anhydride (162) (163) (164) (165). —CHOLATE, prepared from B. with cholic acid (167) (168), or from B-peroxide with cholic acid (165); yellow powder, m. p. 118° to 120° (decomp.). —FERRICHLORIDE, from cotarnine chloride and ferric chloride, orange leaflets, m. p. 104° to 105° (169).

—MONO-α-BROMOISOVALERYLUREIDE, m. p. 127°. —DI-α-BROMOISOVALERYLUREIDE, m. p. 105° to 110°.

COTARNINE-ACETAMIDE: m. p. 135°. —UREIDE, m. p. 180°. —URETHANE, m. p. 110°. —DIETHYLBARBITURATE, m. p. 150°. —PHTHALIMIDE, m. p. 130° (142). COTARNINE ALKYL HALIDES do not exist. (*Cf.* How (45), Beckett and Wright (54).) (*See* cotarninemethine.)

BENZOYL COTARNINE: $C_{12}H_{14}O_4N(COC_6H_5) + \frac{1}{2}H_2O$, white needles from alcohol, m. p. 122° to 123°, insol. in water. —OXIME, m. p. 165° to 166°. —PHENYLHYDRAZONE, crystalline, easily decomposed (105). —ANIL, m. p. 165° (118).

COTARNINE OXIME: $C_{12}H_{15}O_3N{\cdot}NOH$, prisms from alcohol, insol. in water; melts with decomp. at 165° to 168°. Behaves as a weak acid, alkali-soluble. —HYDROCHLORIDE, small yellow needles. —PLATINICHLORIDE, yellow crystalline precip. —MERCURICHLORIDE, white needles from hot water (105).

COTARNINE ANIL: $C_{12}H_{13}O_3N{:}NC_6H_5$, fine needles, m. p. 124°. Similar products are obtained from condensation with p-phenetidine (m. p. 120°) and p-aminobenzoic ester (m. p. 147°) (118).

COTARNINE SULPHIDE: $C_{24}H_{28}O_6N_2S$, m. p. (decomp.) 146° to 148°, insoluble in cold water, decomp. by hot water. Stable toward alkali (125).

COTARNINE PEROXIDE: $C_{24}H_{28}O_8N_2$, from 3% H_2O_2 on cotarnine in methyl alcohol. Decomp. 140°. Insoluble in water. —HYDROCHLORIDE, formed with dry HCl in benzene; water soluble (125).

METHYLENE-DI-COTARNINE: $C_{12}H_{14}O_4N{\cdot}CH_2{\cdot}C_{12}H_{14}O_4N$, from treatment of methylene dinarcotine with HNO_3, decomp. 132°. —DIHYDROBROMIDE ($+H_2O$), decomp. about 240°. —DIHYDRIODIDE ($+H_2O$), decomp. about 235° (86) (166).

BROMOCOTARNINE: $C_{12}H_{14}BrO_4N$, from oxidation of bromohydrocotarnine hydrobromide with Br_2 (70); from dilute HCl solution of cotarnine with excess bromine water, reduction of the superbromide with H_2S and precipitation of the base with NaOH. White needles, decomp. 135°; yields a crystalline hydrochloride, picrate, oxalate, mercurichloride, hydriodide. The BENZOYL derivative is poorly crystallized; the OXIME crystallizes as hydrochloride (106). —HYDROBROMIDE, —PLATINICHLORIDE (70) (104). —ANIL, m. p. 127° (118). BROMOCOTARNINEMETHINE METHIODIDE results from action of methyl iodide on bromocotarnine.

ANHYDROCOTARNINE DERIVATIVES: From condensation of compounds having a reactive methylene hydrogen atom with the aldehyde or carbinol form of cotarnine. They have the general formula $C_{12}H_{14}O_3N{\cdot}R$. —ACETONE, colorless crystals, m. p. 83°; –Hydrochloride, needles decomp. at 171°; –Platinichloride, yellow precip.; –Methiodide, colorless plates, m. p. 144° (107). BENZOYLANHYDROCOTARNINE ACETONE, yellow needles, m. p. 124° (138). —METHYL PROPYL KETONE, m. p. 86° to 92° (107). —ACETOPHENONE, colorless prisms, m. p. 126°; –Methosulphate, 195° to 200°; –Methiodide, m. p. 180°; (139); Anhydromethylcotarnine acetophenone methiodide, yellow needles, m. p. 225° to 226°; Anhydromethylcotarnine acetophenone, leaflets, m. p. 78° (138), compare (139); Acetylanhydrocotarnine acetophenone, $C_{19}H_{17}O_4N(CH_3)(COCH_3)$, yellow needles, m. p. 139° to 140°; Benzoylanhydrocotarnine acetophenone, from alcohol, m. p. 107° to 108° (m. p. 131° to 132° (139)). —ACETYL ACETONE, white prisms, m. p. 98° to 99°; –Hydrochloride and Platinichloride. —ACETONYL ACETONE, white powder, m. p. 147° to 149°; –Hydrochloride and Platinichloride. —ACETOACETIC ESTER, needles from dil. alcohol, m. p. 59° to 60°; –Hydrochloride and Platinichloride. —BENZOYLACETIC ESTER, white needles, m. p. 100° to 102°. —CYANOACETIC ESTER, yellow needles, decomp. 95° to 96°. —ETHYLACETOACETIC ESTER, oily, crystalline Hydrochloride and Platinichloride. —BENZYLACETOACETIC ESTER, oily, solid Hydrochloride and Platinichloride (138). —PHENYLACETIC ESTER, colorless prisms from alcohol, m. p. 91° to 92°;

–Nitrate, –Platinichloride (140); –Methiodide, m. p. 173° to 174°, giving an oily des-N-methyl base whose picrate m. 195° to 196°, platinichloride, 208° to 209°, and methiodide, 197°. Benzoylanhydrocotarnine phenylacetic acid, colorles plates, m. p. 205° to 206° (139). —MALONIC ESTER, white crystalline powder from absolute alcohol, m. p. 73°. With CH_3I gives anhydromethylcotarnine malonic ester methiodide, white needles from water, m. p. 201°. —RESORCIN, m. p. 220°; –Hydrochloride, m. p. 242°. —CUMARONE, amorphous precip. m. p. 66° to 71° (140). —1-HYDRINDONE, prisms, m. p. 126°. —1, 3-DIKETOHYDRINDENE, m. p. 188°. —INDENE, needles, m. p. 136°; –Picrate, m. p. 170°. —FLUORENE, prisms, m. p. 143°; –Picrate, m. p. 183°. —ISATIN, m. p. 146°. —PHENYLACETONITRILE, colorless prisms, m. p. 153° to 155°. With dimethyl sulphate forms a methyl deriv.; Picrate, m. p. 169° to 170°. —α-METHYL INDOLE, m. p. 182° (139). —6-NITROVERATROLE, m. p. not given (143). —PHTHALIDE, from methyl alcohol, needles of m. p. 200° to 201°; Hydrochloride, m. p. 231° to 232°; –Platinichloride, amorph.; –Picrate, 202° to 203°; –Methiodide, 207°. The phthalide has also been named dedimethoxygnoscopine. —5-NITROPHTHALIDE, yellow prisms, m. p. 176° to 177°; –Picrate, 159° to 161°. —5-AMINOPHTHALIDE, flat prisms, m. p. 220° to 221°; Acetylaminophthalide, m. p. 247°. —5-IODOPHTHALIDE, m. p. 173°. —5-HYDRAZINOPHTHALIDE, needles, m. p. 113° to 116°; Benzylidene deriv., m. p. 230° to 232° (141). —2-NITROTOLUENE, yellow prisms, m. p. 75°; –Picrate, m. p. 203° to 205°. —4-NITROTOLUENE, leaflets, m. p. 121° to 122°; –Picrate, m. p. 188° to 190°. —2,6-DINITROTOLUENE, prisms, m. p. 112° to 114°; –Picrate, m. p. 153° to 155°; –Methiodide, m. p. 210° to 212°, giving a des-N-methyl base of m. p. 93° to 95°. —2, 4-DINITROTOLUENE, yellow prisms, decomp. 145° to 146°; –Methiodide decomp., 244° to 245°, giving a des-N-methyl base of m. p. 155°. —2, 4, 6-TRINITROTOLUENE, yellow prisms, expl. at 130°. —NITROMETHANE, prisms from alcohol, m. p. 129°; –Picrate, m. p. 136° to 137°; two Methiodides, m. p. 229° and 199°. —NITROETHANE, methiodide, 216° to 218°; –Picrate, 114° to 116°.

METHYLANHYDROCOTARNINE-O-NITRO-P-TOLUATE, prisms of m. p. 146°; –Picrate, m. p. 163° to 170°; the free acid obtained by hydrolysis gives a picrate of m. p. 183° to 185°. METHYLANHYDROCOTARNINE-2,4-DINITROPHENYLACETATE, black prisms, m. p. 150° to 151°.

DIANHYDROCOTARNINE-2,4,6-TRINITRO-m-XYLENE, yellow prisms, decomp. 153° to 154°. DIANHYDROCOTARNINETRINITROMESITYLENE, m. p. 183° to 185° (137). ANHYDROCOTARNINE METHYLAMINE, from reduction of the nitromethane derivative; –Dihydrochloride, m. p. 227°; –Picrate, m. p. 200° (170). ANHYDROCOTARNINE-NITRO-m-MECONIN, rectangular plates, decomp. 200° (171). ANHYDROCOTARNINE-NITRO-α-METHYLMECONIN, yellow needles, decomp. 160° (172). ANHYDROCOTARNINE-NITROMECONIN, yellow prisms, m. p. 191° (172). (*See* under nitro-β-gnoscopine.) ANHYDROCOTARNINE BENZYLCYANIDE, m. p. 134°; –Hydrochloride, m. p. 154° to 155° (133).

6-NITROPIPERONYLIDENE HYDROCOTARNINE, yellow prisms from methyl alcohol, m. p. 112°; –Picrate 175°. BENZYLIDENE HYDROCOTARNINE, from benzyl magnesium chloride on oxycotarnine, quadratic prisms m. p. 135°; –Picrate 133°. 6-NITROPIPERONOYL HYDROCOTARNINE, m. p. 172°; –Picrate 247° to 248° (143) (173). ACETYLCOTARNINE ACETIC ACID (108), first named acetyl hydrocotarnine acetic acid (89), from refluxing cotarnine with acetic anhydride, pale yellow needles, m. p. 201°; salts; ethyl ester, m. p. 113°; structure, Roser (60), Liebermann (107), Ahlers (174). Reduction with sodium amalgam in presence of CO_2 gives acetylhydrocotarnine acetic acid $C_8H_6O_3(CH_2CH_2CO_2H)$ $(CH_2CH_2NCH_3COCH_3)$, m. p. 178°. (108) (174). ACETYLCOTARNINE-DIBROMOACETIC ACID, m. p. 188°. ACETYLBROMOCOTARNINE ACETIC ACID, prep. like bromine-free compound, may be saponified to BROMOCOTARNINE ACETIC ACID ($+4\frac{1}{2}$ H_2O) m. p.

165°, anhydr. 189°; this reduces with sodium amalgam to HYDROBROMOCOTARNINE ACETIC ACID, dec. 184°; salts (108). HYDROCOTARNINE ACETIC ACID, (89) (174), m. p. 116°; –Methyl ester, from methyl alcohol, m. p. 63°; –Methyl ester methiodide, m. p. 119°. N-ACETYLCOTARNINE (174), from acetylcotarnine acetic acid by $KMnO_4$ oxidation, m. p. 146°; –Oxime, m. p. 156°. BENZOYLCOTARNINE ACETIC ACID (174), from benzoylcotarnine and acetic anhydride; –Ethyl ester, m. p. 81°.

TETRASODIUM COTARNINE; $C_{12}H_{11}O_4NNa_4$, from refluxing cotarnine with sodium in benzene. A hygroscopic yellow powder, sol. in water, alcohol, $CHCl_3$ (175).

OXYCOTARNINE: $C_{12}H_{13}O_4N \cdot H_2O$, from oxidation of cotarnine with potassium permanganate; colorless prisms from dil. alcohol, m. p. 69° to 70°, anhydrous, m. p. 108°. —AURICHLORIDE, m. p. 160°. —PLATINICHLORIDE, orange plates, m. p. 179° to 180°. OXY-5-BROMOCOTARNINE, from the action of HBr on oxycotarnine, silvery needles, m. p. 125° to 126° (110) (176).

COTARNMETHYLIMIDE: $CH_2O_2C_6H(OCH_3)\begin{<}CO\\CO\end{>}NCH_3$, from oxidation of cotarnine in alkaline solution with potassium permanganate; fibrous needles from alcohol, sublime at 190° to 195°, decomp. 205° to 206° (176). COTARNIMIDE: $C_{11}H_{11}O_3N$, was obtained by oxidation of nornarcotine with ferric chloride (59).

COTARNONE: $C_8H_6O_3\begin{<}CH{=}CH_2\\CHO\end{>}$, is formed by the action of alkali on cotarninemethine methochloride; rhombic plates from alcohol, m. p. 78°; –Oxime, needles, decomp. 130° to 132° (60) (118). BROMOCOTARNONE, similarly from bromocotarninemethine methiodide (106); –Phenylhydrazone, decomp. 204°; α-Oxime, 125° to 126° and again at 190° (the β-oxime); acetyl compound from oxime, m. p. 107° and 173° (loses acetic acid, forming methoxymethylenedioxybromoisoquinoline). Treatment of cotarninemethine methochloride with acetic anhydride gives cotarnone acetic acid (108) (*cf.* acetylcotarnine acetic acid); at the same time, a polymer of cotarnone is formed. COTARNONE NITRILE: $C_8H_6O_3\begin{<}CH{:}CH_2\\CN\end{>}$, from cotarninemethine methochloride with hydroxylamine hydrochloride and then with alkali. White needles, m. p. 160°; –Dibromide, yellow prisms, m.p. 140° (105). COTARNLACTONE: $C_8H_6O_3\begin{<}CH\cdot CH_2OH\\COO\end{>}$, from slow oxidation of cotarnone with potassium permanganate. Oblique prisms, m. p. 154°; with alkali yields cotarnlactone acid, leaflets, decomp. 90° to 100°; barium salt, needles from dil. alcohol. COTARNIC ACID (Methoxyhydrastic acid): $C_8H_6O_3(CO_2H)_2$, from oxidation of cotarnine (110) or cotarnone (60) with potassium premanganate. Synthetic (111). Plates from water, m. p. 178°, forming the anhydride of m. p. 161° to 162°; barium, potassium, and silver salts (60). The cotarnic acid $C_{11}H_{12}O_5$ of Matthiessen and Foster (46) has never been confirmed (70) (114). COTARNAMIC ACID. —HYDROCHLORIDE, $C_{11}H_{11}O_3N \cdot HCl \cdot H_2O$, yellow silky needles, from action of conc. hydrochloric acid on cotarnine (104). (*Cf.* (46) (103).)

COTARNINEMETHINE: $C_8H_6O_3\begin{<}(CH_2)_2N(CH_3)_2\\CHO\end{>}$, in the form of its methiodide is the product from the action of methyl iodide on cotarnine. Yellow needles (60) (118). Methochloride, shining flakes containing $3H_2O$. Platinum, mercury

salts (60). A nitrile methochloride is formed by action of hydroxylamine hydrochloride on the methine methochloride. Crystallized from alcohol with $2\frac{1}{2}H_2O$ (105). BROMOCOTARNINEMETHINE METHIODIDE (106), yellow bundles of needles, from bromocotarnine and methyl iodide; -Methochloride $+2\frac{1}{2}H_2O$, acute triclinic prisms; -Methobromide, plates decomp. 200°. Excess of bromine on cotarninemethine methochloride gives dibromocotarnine ethyltrimethylammonium bromide with loss of CO_2, decomp. 245°; with NaOH, it forms dibromocotarnvinyl, needles, m. p. 83.5°; Dibromo derivative m. p. 126°. COTARNOLINE: $C_6H(OH)_3\begin{matrix}CH_2CH_2\\ |\\ CH{:}NCH_3\end{matrix}$, is formed as sulphate by heating cotarnine chloride with aluminum chloride to 150° and treating with ice and sulphuric acid. Greenish yellow needles (from 5% H_2SO_4) decomp. 265° to 270°, soluble in alkali (150).

NORCOTARNINE:[53] $C_8H_6O_3\begin{matrix}CH_2{-}CH_2\\ |\\ CH{=}N\end{matrix}$, has been obtained by synthesis. Oily crystals, picrate m. p. 182° to 184°. With methyl iodide gives cotarnine iodide (145). NORCOTARNINEMETHINE (METHIODIDE): $C_7H_4O_3\begin{matrix}(CH_2)_2N(CH_3)_3I\\ CHO\end{matrix}$ results from reaction of cotarnine anil and methyl iodide; yellow needles, m. p. 272°. With alkali it gives norcotarnone, m. p. 89°, whose oxime m. 202° to 203°. BROMONORCOTARNINEMETHINE METHIODIDE, m. p. 264° from bromocotarnine anil. The methiodide with alkali gives bromonorcotarnone, m. p. 138° (118).

DIDEHYDROCOTARNINE. —CHLORIDE: $C_{12}H_{12}O_3NCl+1\frac{1}{2}H_2O$, decomp. 205° to 208°, yellow needles, from oxidation of narcotine with mercuric acetate; -Mercurichloride, m. p. 225°; -Aurichloride, m. p. 151°; -Platinichloride decomp. 220° to 225°; -Picrate, m. p. 180°; -Triiodide, m. p. 161°. The chloride on catalytic reduction gives hydrocotarnine. Didehydro-acetocotarnine chloride, decomp. 120° from mercuric acetate oxidation of acetonarcotine (36).

NEOCOTARNINE, 2-methylaminoethyl-4-methoxy-5, 6-methylenedioxybenzaldehyde, an isomer of cotarnine obtained by synthesis, colorless prisms decomp. 124°; -Aurichloride, decomp. 127°; -Picrate, sinters 90°, m. p. 100° (144).

TARCONINE

METHOXYMETHYLENEDIOXYBROMOISOQUINOLINE: $C_{11}H_8O_3NBr$, an isomer of N-methylbromotarconine, is formed from bromocotarnone-α-oxime acetyl derivative by loss of acetic acid on melting; m. p. 173°; cryst. HYDROCHLORIDE and PLATINICHLORIDE; the METHIODIDE, m. p. 203°, is identical with methyl-N-methylbromotarconium iodide. The ETHIODIDE decomp. 179° (methyl-N-ethylbromotarconium iodide).

N-METHYLTARCONINE: $C_{11}H_9O_3N$, from bromocotarnine bromide by heating to 190° to 210° (70), or from heating methyl-N-methyltarconium iodide with hydrochloric acid (67); white cryst. insol. in water. —PLATINICHLORIDE is crystalline.

N-METHYLBROMOTARCONINE: $C_{11}H_8O_3NBr+2H_2O$, from heating bromocotarnine superbromide. Red needles, decomp. 235° to 238°, sol. in hot water. —HYDROBROMIDE, yellow crystals decomp. 280°. —HYDROCHLORIDE, yellow crystals. —PLATINICHLORIDE (70) (115).

[53] The nomenclature at this point is confused, since norcotarnine has been previously used (118) for a cotarnine demethylated on oxygen.

N-METHYLIODOTARCONINE: $C_{11}H_8O_3NI + H_2O$, from heating methyl-N-methyliodotarconium iodide, orange needles. —HYDROCHLORIDE ($+2H_2O$), yellow needles (67).

METHYL-N-METHYLTARCONIUM. —Derivatives. —IODIDE: ("tarconine methiodide") $C_{11}H_9O_3N{\cdot}CH_3I$, from methyl-N-methyltarconine superiodide ("tarconine triiodide") by removal of iodine with hydrogen sulphide (48) (67) (147), or from iodine oxidation of cotarnine and hydrocotarnine, yellow needles of m. p. 192° (90). With silver oxide it gives the amorphous ammonium base (105). —SUPERIODIDE: $C_{11}H_9O_3NCH_3I{\cdot}I_2$, red-brown needles, m. p. 160° (48) (67). —HEPTAIODIDE: $C_{11}H_9O_3NCH_3I{\cdot}I_6$, metallic green crystals from the superiodide with iodine (48). —CHLORIDE (48) (67) and its PLATINICHLORIDE, AURICHLORIDE, and MERCURICHLORIDE, as well as numerous other double salts are known. —ACID SULPHATE: $C_{11}H_9O_3NCH_3HSO_4$, yellow crystals (90).

METHYL-N-METHYLBROMOTARCONIUM. —IODIDE: ("bromotarconine methiodide") $C_{11}H_8O_3NBr{\cdot}CH_3I$, from N-methylbromotarconine and methyl iodide, or from methoxymethylenedioxybromoisoquinoline with methyl iodide (106), yellow needles, m. p. 203° to 204°. —CHLORIDE, PLATINICHLORIDE, AURICHLORIDE, MERCURICHLORIDE (67) (117). —BROMIDE: $C_{11}H_8O_3NBr{\cdot}CH_3Br + H_2O$, from methyl-N-methyltarconium chloride with bromine; a superbromide, yellow plates, decomp. 165°, is first formed, which reduces with H_2S to the bromide, yellow needles (67).

METHYL-N-METHYLIODOTARCONIUM. —IODIDE: ("iodotarconine methiodide") $C_{11}H_8O_3NI{\cdot}CH_3I$, by action of iodine on narcotine; –Superiodide, m. p. 171° (67). —CHLORIDE, PLATINICHLORIDE and AURICHLORIDE (yellow needles) (67).

ETHYL-N-METHYLBROMOTARCONIUM IODIDE: $C_{11}H_8O_3NBr{\cdot}C_2H_5I$, from N-methylbromotarconine and ethyl iodide, light yellow needles, m. p. 205° to 206° (117).

AMYL-N-METHYLBROMOTARCONIUM IODIDE, yellow needle clumps (117).

METHYL-N-ETHYLBROMOTARCONIUM. —IODIDE: (Methoxymethylenedioxybromoisoquinoline ethiodide) $C_{13}H_{13}O_3NBrI$, from the isoquinoline base with ethyl iodide, short yellow needles from water, decomp. 179°. —CHLORIDE, decomp. 133°. —PLATINICHLORIDE, m. p. 227° (106).

N-ETHYLBROMOTARCONINE: $C_{12}H_{10}O_3NBr + 2H_2O$, by loss of methyl chloride from methyl-N-ethylbromotarconium chloride at 100°; orange-red needles from hot water, darken over 100°, melt at 187°; anhydrous, dark red. —HYDROCHLORIDE, yellow needles. —PLATINICHLORIDE, orange plates, decomp. 215° to 220° (106).

ETHYL-N-ETHYLBROMOTARCONIUM. —IODIDE: $C_{14}H_{15}O_3NBrI$, from N-ethylbromotarconine with ethyl iodide, yellow prisms from water, decomp. 212°. —CHLORIDE, needle bundles. —PLATINICHLORIDE, decomp. 236° (106).

METHYL-N-METHYL-1-PHENYLHYDROTARCONINE: $C_{18}H_{17}O_3N$, from phenylmagnesium bromide and methyl-N-methyltarconium iodide; white crystals of m. p. 102° (135) (148).

METHYL-N-METHYLTARCONINIC ACID: $C_{11}H_{11}O_3N + 2H_2O$, is formed through loss of formaldehyde on heating methyl-N-methyltarconium hydroxide with barium hydroxide; yellow needles of m. p. 244°. Forms a HYDROCHLORIDE and SULPHATE (105).

METHYL-N-METHYLPSEUDOTARCONINIC ACID: $C_{11}H_{11}O_3N$, from heating methyl-N-methyltarconium hydroxide with water; forms a HYDROCHLORIDE and two SULPHATES (67). (*Cf.* Roser (105).)

METHYL-N-METHYLBROMOTARCONINIC ACID: $C_{11}H_{10}O_3NBr + 2H_2O$, preparation like that of the analogous tarconinic acid. Yellow prisms of m. p. 233°, forming crystalline sodium or copper salts, crystalline hydrochloride, and platini-

chloride. The acid gives a violet color with ferric chloride on warming (67) (117). A monoacetyl derivative is obtained with acetic anhydride.

ETHYL-N-METHYLBROMOTARCONINIC ACID: $C_{12}H_{12}O_3NBr+2H_2O$, is formed like the methyl compound; decomp. 223° to 224°. Barium and copper salts, and the PLATINICHLORIDE were prepared. —HYDROCHLORIDE, yellow needle bundles (117).

METHYL-N-ETHYLBROMOTARCONINIC ACID: $C_{12}H_{12}O_3NBr$, by loss of formaldehyde from methyl-N-ethylbromotarconium iodide on treatment with $Ba(OH)_2$; yellow prisms, decomp. 210°. Barium salt $+3\frac{1}{2}H_2O$. —HYDROCHLORIDE $+2H_2O$, white needles (106).

ETHYL-N-ETHYLBROMOTARCONINIC ACID: $C_{13}H_{14}O_3NBr$, from the corresponding tarconium compound with $Ba(OH)_2$; yellow prisms from dilute alcohol, decomp. 205° to 206°.

TARCONIC ACID: $C_{10}H_7O_3N$, is formed from ethyl- or methyl-N-methylbromotarconinic acid by heating with conc. HCl at 160° five hours, isolated as the hydrochloride in brownish star-grouped prisms; hydrated form, yellow needles. The free base has not been obtained pure, but behaves like nartinic acid (117). In the same reaction, Gasser (108) obtained "methylchlorotarconol", apparently N-methylchlorotarconinic acid, by exchange of chlorine for bromine (compare similar behavior of halogen naphthoquinone derivatives) and loss of the O-methyl group as methyl chloride. Diacetylmethylchlorotarconol acetate melts with decomp. about 205°. Treatment of methyl-N-methylbromotarconinic acid with HBr at 160° yielded "methylbromotarconol" (N-methylbromotarconinic acid), decomp. 160°.

NARTINIC ACID (Nartine): $C_{20}H_{16}O_6N_2$ (?), is formed together with CO and CO_2 by the action of conc. HCl on N-methylbromotarconine, or on tarnine, at 130°. —HYDROCHLORIDE, yellow needles, from which the free base is obtained as an orange ppt., decomp. under 200° without melting. Amorphous copper, barium and calcium salts are known (104) (117).

TARNINE: $C_{11}H_9O_4N+1\frac{1}{2}H_2O$ (?), orange-red needles obtained from heating bromotarconine (or cupronine) in water at 130°. Does not melt at 290°. —HYDROCHLORIDE, yellow star-grouped crystals (104) (117).

CUPRONINE: $C_{20}H_{18}O_6N_2$ (?), formed with tarnine by heating bromotarconine salts in water at 130°; a black powder. —HYDROCHLORIDE and HYDROBROMIDE, copper-colored needles (104) (117).

CUPRINE: $C_{11}H_7O_3N$; $(C_{22}H_{14}O_6N_2)$, concentric-grouped coppery needles, obtained from the hydrobromide, which is formed by the action of bromine-water on N-methylbromotarconine; decomp. above 280°. —HYDROCHLORIDE, brown metallic needles. —PLATINICHLORIDE, blue precip. (115).

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GNOSCOPINE

This alkaloid was first isolated in the factory of T. and H. Smith (1) (1878) out of the mother liquors from narcotine preparation. Analysis showed its formula to be $C_{22}H_{23}O_7N$ (2), isomeric with narcotine. The investigations of Rabe (3) (4) (5) and of Perkin and Robinson (6) (7) (8) have proved that it is r-narcotine, probably formed by

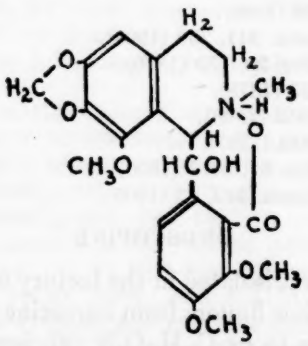
racemization of the optically active alkaloid during the chemical operations involved in its isolation from opium (4).[54]

Gnoscopine crystallizes from alcohol in white woolly needles (1); m. p. 232° to 233° with decomposition (1) (5). It is soluble in cold alcohol 1:1,500 (1), sparingly soluble in benzene, easily soluble in hot chloroform or carbon disulphide; insoluble in water or dilute alkali. In alcoholic solution it turns red litmus; it forms crystalline salts which hydrolyze in aqueous solution with reformation of the base (5). Gnoscopine is optically inactive (3) (5). Its absorption spectrum is identical with that of narcotine (9).

Gnoscopine may be prepared from narcotine by heating the latter with 15 parts of absolute alcohol at 175° for 6 hours in a sealed tube; 10 g. of narcotine gave 2.5 g. of gnoscopine. Narcotine is likewise converted in part to gnoscopine by refluxing for 8 days in 50% alcohol (5). The racemization also takes place on heating narcotine with barium hydroxide, but not with 10% sulphuric acid (4). Frerichs (10) accomplished the change by heating narcotine to 200° in an indifferent medium (urea). Ordinary (α) gnoscopine is formed in small amounts by long heating of the isomeric β-gnoscopine at 100° (11).

The resolution of gnoscopine was attempted by Rabe and McMillan (5), who obtained a quaternary bromocamphorsulphonate which could be crystallized into fractions of different rotatory power. Using *d*-bromocamphorsulphonic acid, Perkin and Robinson (6) separated natural gnoscopine into *l*- (natural) narcotine and the new *d*-narcotine.

In most of its chemical reactions, gnoscopine is identical with narcotine. Oxidation with dilute nitric acid gives cotarnine, opianic acid, and teropiammon (5) (6). Gnoscopine methiodide, on treatment with alkali yields narceine (6) (10). On long continued boiling with dilute acetic acid, gnoscopine is converted to nornarceine, cotarnine and meconin (3) (4). The sodium salt of gnoscopine, in contrast to that of narcotine, can not be isolated; if, however, the reaction mixture of gnoscopine and sodium hydroxide is treated with an amount of acid equivalent to the alkali present, the inner salt of a hydroxy-acid separates.



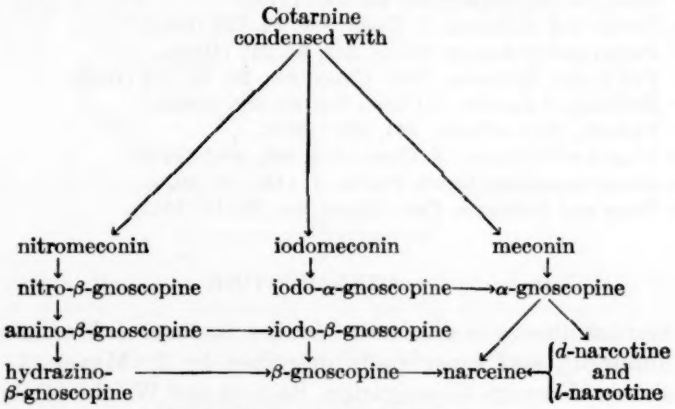
[54] T. and H. Smith & Co. showed as early as 1893 (2) that when narcotine was heated to 130° with acetic acid it was converted in part to gnoscopine.

This is easily changed back to gnoscopine by loss of water (4).

Gnoscopine was synthesized by Perkin and Robinson (6) (8) (1910) through condensation of cotarnine and meconin. (See under narcotine.) The product was in every way identical with the gnoscopine obtained from opium extraction.

The presence of two asymmetric carbon atoms in narcotine predicts its existence in two inactive forms; natural gnoscopine represents one of these, and β-gnoscopine is probably the other (11).

Cotarnine and nitromeconin condense easily to form nitrognoscopine (anhydrocotarninenitromeconin). Elimination of the nitro group (through the hydrazino- or iodo- compounds) results in β-gnoscopine, of m. p. 180°. The isomerism of α- and β-gnoscopine persists through a number of derivatives; the relationships are shown by the following diagram of Hope and Robinson (11):



β-Gnoscopine has not been resolved into optical isomers.

Descriptive Part (Gnoscopine)

GNOSCOPINE, —HYDROCHLORIDE (5) (11): From the action of alcoholic HCl, conc. aqueous HCl, or HCl in glacial acetic acid; colorless needles, m. p. 238° to 241° (decomp.). —PLATINICHLORIDE (6), amorphous, yellow. —AURICHLORIDE (6), amorphous, colorless. —MERCURICHLORIDE (6), amorphous buff precipitate. —METHIODIDE (10), prepared by refluxing in alcohol 8 hours with excess CH_3I, decomp. ca 168° (5); $+2H_2O$, prisms which easily lose water, giving the anhydrous compound, m. p. 210° to 212° (6). —PICRATE (5) (6), m. p. 188° to 189° (185.5° corr. (12)). —PICRONOLATE (5), yellow-brown decomp. 232°. GNOSCOPINE-METHYLBROMOCAMPHORSULPHONATE (5), optical properties described.

CHLOROGNOSCOPINE (6): From condensation of chloromeconin with cotarnine, colorless needles, m. p. 187°. —PICRATE, m. p. ca. 201°. BROMOGNOSCOPINE (6), prisms from alcohol, m. p. 188° to 189°; —PICRATE, m. p. 206°. IODOGNOSCOPINE (6), prisms from alcohol, m. p. 170°; —METHIODIDE, m. p. 190° to 195°.

β-GNOSCOPINE (11) (13); $C_{22}H_{23}O_7N$, is formed by oxidation of hydrazino-β-gnoscopine with cold copper acetate, or quantitatively by reduction of iodo-β-gnoscopine with aluminum amalgam in hot methyl alcohol; colorless rectangular prisms from ethyl acetate, methyl or ethyl alcohol; m. p. 180°. —HYDROCHLORIDE, colorless prisms, freshly prepared m. at 86° to 88°, after drying, m. p. 224° to 226°. —NITRATE, microscopic prisms. —PICRATE, m. p. 199° to 201° (decomp.). —METHOSULPHATE, resinous, is converted to narceine by hot KOH.

NITRO-β-GNOSCOPINE (11) is obtained in 90% yield by boiling nitromeconin and cotarnine in methyl alcohol 10 minutes; recrystallized from trichloroethylene. Yellow prisms, m. p. 191°. —HYDROCHLORIDE, dec. 142° to 143°. —METHIODIDE, m. p. 204° to 206°. —PICRATE, m. p. 153°. AMINO-β-GNOSCOPINE, in 75% yield by reduction of the nitro compound in acetic acid with stannous chloride. Colorless prisms from ethyl acetate, m. p. 205°; acetyl derivative, m. p. 198°. For other derivatives see original. Diazotization of the amino compound and treatment with KI gives IODO-β-GNOSCOPINE, m. p. 185°. —PICRATE, m. p. 189° to 190°.

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(3) Rabe, Ber. **40**, 3280 (1907).
(4) Rabe and McMillan, Ann. **377**, 223 (1910).
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(6) Perkin and Robinson, J. Chem. Soc. **99**, 775 (1911).
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OXYNARCOTINE

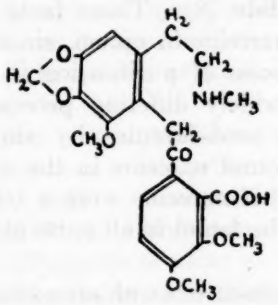
Oxynarcotine was discovered in the factory of Macfarlan & Co. (Edinburgh), and superficially described by L. Mayer (1) in 1871. In a more thorough investigation, Beckett and Wright (2) determined its formula to be $C_{22}H_{23}O_8N$.

Oxynarcotine was found as granular crystals in crude narceine, from which it was separated by dissolving the mixed bases in hot dilute sulphuric acid and adding the equivalent amount of sodium hydroxide; the pulplike mass of narceine crystals so obtained, on boiling with successive small quantities of water, went into solution, leaving undissolved the small hard crystals of oxynarcotine (2). There seems to be no other record of its separation from opium.

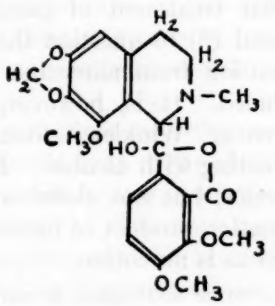
Oxynarcotine forms minute micaceous sandy crystals, resembling somewhat those of narcotine. It is slightly soluble in boiling water or alcohol, practically insoluble in benzene, ether, or chloroform. It is precipitated from solutions of its salts by alkali or alkali carbonates; the base seems to be slightly soluble in alkalies. The hydrochloride, like those of narcotine and narceine, forms a series of basic salts when treated with boiling water.

Of the structure of oxynarcotine nothing is known with certainty; it must resemble closely that of narcotine. Beckett and Wright found that the base was converted by oxidizing agents to cotarnine and hemipinic acid, from which they inferred that narcotine and oxynarcotine were related as aldehyde to acid. Roser (5) believed it to be a derivative of opianylhydrocotarnine (narcotine). Rabe

and McMillan (3), from a comparison of the properties of oxynarcotine and nornarceine, and a consideration of Beckett and Wright's analytical results, hold that these two substances are identical. Differences in solubility and in the water of crystallization held by the two bases and their hydrochlorides make it seem doubtful that they are the same; oxynarcotine is perhaps formed from narcotine by gentle oxidation, although attempts to accomplish this change have failed. (Gadamer and Von der Bruck (4).)



Oxynarcotine (Nornarceine) (3)



Oxynarcotine (4)

Oxynarcotine Derivatives

OXYNARCOTINE ($B=C_{22}H_{23}O_8N$). —HYDROCHLORIDE: $C_{22}H_{23}O_8N \cdot HCl + 2H_2O$, crystal mass of paper pulp consistency from hot dil. HCl; boiling with water gives compounds of the type B_5HCl and B_7HCl (compare narcotine and narceine hydrochlorides). —PLATINICHLORIDE $(C_{22}H_{23}O_8N \cdot HCl)_2PtCl_4$. (See also Nornarceine.)

Bibliography (Oxynarcotine)

(1) L. Mayer, Proc. Phil. Soc. Glasgow, 1871.
(2) Beckett and Wright, J. Chem. Soc. **29**, 461 (1876).
(3) Rabe and McMillan, Ann. **377**, 223 (1910).
(4) Gadamer and Von der Bruck, Arch. Pharm. **261**, 117 (1923)
(5) Roser, Ann. **254**, 334 (1889).

NARCEINE

Narceine, $C_{23}H_{27}O_8N \cdot 3H_2O$, was discovered in 1832 by Pelletier (1), who obtained it as white silklike needles from the aqueous extract of opium, after the removal of narcotine, morphine, and meconic acid. From its decomposition by heating, he obtained a minute quantity of crystals which he believed to be gallic acid.[55]

Narceine occurs in opium to the extent of about 0.1 to 0.4% (2) (in Japanese opium 0.2 to 0.5%) (3). Dawson (4), on the basis of qualitative tests, believes to have found it in the fruit of *Diervilla florida* (bush honeysuckle).[56]

[55] The relationship of the α-benzyltetrahydroisoquinoline alkaloids to gallic acid was first definitely shown by Roser, Ann. **254**, 334 (1889). See cotarnic acid.

[56] The fruit which Dawson describes is not that of *Diervilla*, but rather of the family *Lonicera*.

The mother liquors from the preparation of morphine hydrochloride (Gregory procedure) are treated with ammonium hydroxide as long as a precipitate forms, the precipitate (resins, narcotine, and thebaine) immediately filtered out, and the filtrate treated with lead acetate. The filtrate from this precipitation is freed from lead with sulphuric acid, excess sulphuric acid neutralized with ammonia, and the solution allowed to concentrate at a moderate temperature. The crystals separating are purified by alternate crystallizations from water and alcohol (5).

Narceine is prepared in the laboratory from narcotine by treatment of narcotine methochloride with alkali and steam (6) (7)[57] or by similar treatment of gnoscopine methiodide (8). These facts led Freund (9) to question the existence of narceine in opium, since its formation from narcotine during the process of purification is not excluded. It is, however, obtained in widely differing processes; moreover, Winkler [58] found it in poppy seed-capsules by simply extracting with alcohol. Kerbosch (10) found narceine in the seed-capsules, but not elsewhere in the plant; if narceine were a transformation product of narcotine, it should be found in all parts of the plant as is narcotine.

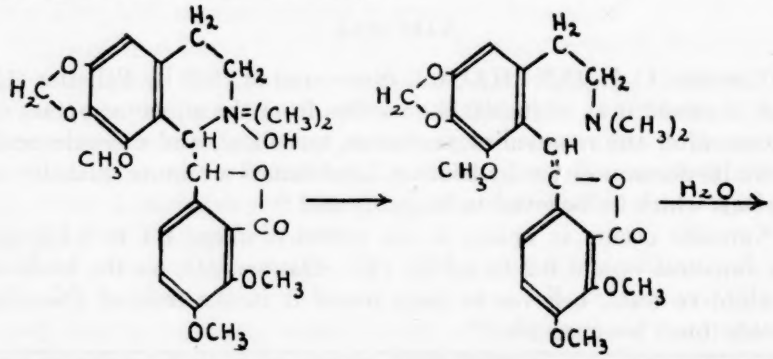
Narcotine methiodide is converted to the methochloride with silver chloride (6), or better with chlorine-water (7), the methochloride treated with the equivalent amount of sodium hydroxide, and a vigorous current of steam passed into the solution. On cooling, the liquid becomes a mass of feltlike crystals. The yield of methochloride (chlorine-water method) is from 50 to 60%; conversion of this to narceine is nearly quantitative. The action of chlorine on narcotine methiodide results in the formation of about 33% narcotine-methyl triiodide:

$$3\ C_{22}H_{23}O_7N\cdot CH_3I + 2\ Cl_2 \longrightarrow 2\ C_{22}H_{23}O_7N\cdot CH_3Cl + C_{22}H_{21}I_2O_7N\cdot CH_3I + 2HCl$$

The formation of narceine from narcotine methohydroxide is analogous to the Hofmann and Ladenburg [59] opening of a piperidine ring (6), with simultaneous hydrolysis of a lactone group.

$$C_{22}H_{23}O_7N\cdot CH_3OH + 3H_2O \longrightarrow C_{23}H_{27}O_8N\cdot 3H_2O$$

The structure of narceine has been shown chiefly by the researches of Roser and of Freund. The following mechanism is accepted for its preparation from narcotine (9).



[57] It has been shown recently (Rodionov, Bull. soc. chim. 39, 305 (1926)) that a nearly quantitative yield of narceine is obtained by boiling narcotine and methyl-p-toluenesulphonate in dilute sodium hydroxide.

[58] Original could not be located. See Freund, Ann. 277, 30, note 28 (1893).

[59] Hofmann and Ladenburg, Ber. 16, 2057 (1883).

Although the hypothetical intermediate substances in this reaction can not be isolated, the assumption of their existence is justified, since in the case of the closely related hydrastine the reaction proceeds stepwise (31).

Narceine crystallizes from water or alcohol in white silky needles (1) or long white prisms (11). The hydrated base melts at 170° to 171° (12), is soluble in hot alcohol or much boiling water, and is insoluble in chloroform, benzene, or ether (9). One part dissolves in 1,285 parts of water at 13° (13). It is soluble in alkali or ammonia, but insoluble in sodium carbonate, and is precipitated from its solution in alkali by carbon dioxide. It is a very weak base and does not affect litmus (14) (15)[60] or phenolphthalein, but turns helianthin yellow (16). It is likewise a weak acid, as is shown by the low heat of formation of its potassium salt; the indicator C4B (Poirrier Blue), reddened by KOH, is turned by the carboxyl group (15) (16). At 100° it loses $3H_2O$ to give the anhydrous base (6), which melts at 140° to 145° (145.2° corr. (13)), and is soluble in benzene or chloroform but not in ether. It is very hygroscopic, and slowly takes water from even calcium chloride (9). It can not be sublimed (17) (18). Narceine in alcoholic, alkaline, or acid solution is optically inactive (19).[61] The absorption spectrum has been determined (21) (22) (23).

Solid narceine with potassium iodide-iodine solution gives an intense blue color (24) (25), which is destroyed by those media which dissolve narceine. From its colorless solution in boiling water the blue substance separates again unchanged (26). None of the other opium alkaloids give this reaction. Narceine in solution may be so detected if potassium-zinc iodide is also present. The reaction is sensitive to one part of narceine in 2,500 parts of water (in the presence of a little ether) (24). Narceine with chlorine-water and a little ammonia gives a blood-red coloration (27). Plugge (14) (28) describes other very sensitive color reactions of narceine. Further more or less characteristic tests are given by Reichard (29) and David (30). Kerbosch (10) gives the sensitivity of 69 reagents for the opium alkaloids.

Anderson, from analyses of the free base, its hydrochloride and platinichloride, first put forward the empirical formula $C_{23}H_{29}O_9N \cdot 2H_2O$ (5), which was confirmed by analyses of Beckett and Wright

[60] According to Merck (12) a hot conc. solution of narceine (free from hydrochloride) reacts weakly basic to litmus. Narceine hydrochloride is completely dissociated in aqueous solution (20).

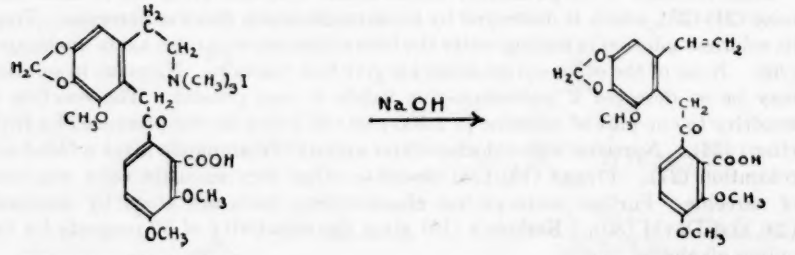
[61] Bouchardat and Boudet, J. pharm. chim. (3) **23**, 292 (1853), who found optical activity, were evidently working with impure material. The slight rotation (levo) which they observed could easily have been due to foreign material, since natural narceine is obtained free from traces of other opium alkaloids only with the greatest difficulty. (*Cf.* Merck (12).)

(32), Hesse (13), and Claus and Meixner (33). It remained for Roser (6) in 1888 to show that "pseudonarceine", the degradation product from narcotine methiodide, which he believed to be identical with natural narceine, had the formula $C_{23}H_{27}O_8N \cdot 3H_2O$. The identity of narceine and pseudonarceine was established by Freund and Frankforter (9) (60), who by analysis of the salts of narceine with alkali-metals showed these to be derived from a substance having the formula $C_{23}H_{27}O_8N$ instead of the Anderson formula $C_{23}H_{29}O_9N$. Numerous determinations on natural narceine showed that it contained three molecules of water, two of which were lost with ease, the third only with great difficulty.[62] [63]

Attempts to determine the structure of narceine by oxidation met with but little success. Oxidation with potassium dichromate and sulphuric acid, or with ferric chloride, yielded hemipinic acid and methylamine, but no opianic acid (53). Since opianic acid is not oxidized to hemipinic acid by ferric chloride, this indicated that the opianyl radical is not present in narceine.[64]

By oxidation with potassium permanganate, Claus and Meixner (33) obtained small quantities (at best 8% of the weight of starting material) of a tribasic acid, narceinic acid, $C_{15}H_{18}O_8N \cdot 3H_2O$. At 180° to 200° narceinic acid breaks up into carbon dioxide, dimethylamine, and a dihydroxynaphthalene dicarboxylic acid of m. p. 162°. Freund (9) was not able to repeat this experiment, and believes that narceinic acid was derived from impurities in the narceine.

Narceine contains three methoxyl groups (9) and two N-methyl groups (34), which shows that the nitrogen is not part of a ring. That it is tertiary and stands at the end of an open chain is evident, since treatment of narceine methiodide with alkali results in loss of trimethylamine and formation of narceonic acid (9).[65] This is monobasic, and still contains the carbonyl group, since it forms oxime- and phenylhydrazone-anhydrides.



Narceine Methiodide — Narceonic Acid

[62] *Cf.* Hesse, Ber. 7, 105 (1874).

[63] Leroy (15) claims to have worked with a dihydrate $C_{23}H_{27}O_8N \cdot 2H_2O$, which on recrystallization from water was converted to the trihydrate. Evaporation of an aqueous solution of narceine at 100° gave a monohydrate (16).

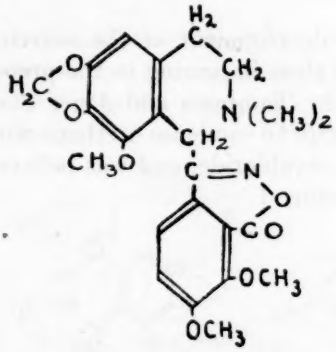
[64] Claus and Meixner (33) could obtain no hemipinic acid by oxidation of pure narceine (m. p. 162°) with $FeCl_3$; it seemed to be unaffected by the reagent. (*Cf.* also Roser (6).)

[65] Claus and Ritzefeld, Ber. 18, 1569 (1885), by the action of boiling alkali on narceine alkyl halides, obtained alkali halide and alkyl narceines. Narceine methiodide and narceine benzochloride yielded, respectively, methylnarceine and benzylnarceine. Freund (9) was unable to duplicate this, obtaining in every case narceonic acid.

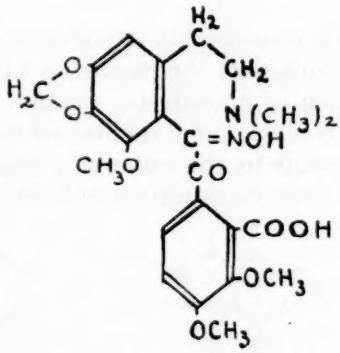
Narceine is a monobasic acid, and dissolves readily in alkalies, yielding well-crystallized salts (9) [66] which may be used to purify the alkaloid (60). It is esterified by alcoholic HCl (9) (35), or by methyl iodide and sodium methylate (36) (with formation of the ester methiodide).

Narceine-sodium reacts with dialkyl sulphates (57) (59), or alkyl halides (58) with production of alkyl-narceines in which the carboxyl group is still free; these compounds add alkyl halides on nitrogen, and may be esterified like narceine itself.

The carbonyl group of narceine reacts readily with phenylhydrazine or hydroxylamine, giving the phenylhydrazone- or oxime- anhydrides. From the oxime anhydride with potassium hydroxide, the oxime itself may be obtained (9).*



Narceine-oxime Anhydride



Isonitrosonarceine

The presence of the grouping $-CH_2CO-$ in narceine is shown by its ability to react with ethyl nitrite [67] to form isonitrosonarceine (35). With methyl iodide and alcoholic KOH, this alkylates to isonitrosonarceine-methyl-ester-N-methyl-ether methiodide, which, treated further with alkali, decomposes to trimethylamine, hemipinic acid, and 1-vinyl-2-cyan-3-methoxy-4,5-methylenedioxybenzene.[68] This compound is likewise obtained, together with hemipinic acid and dimethylamine by heating isonitrosonarceine itself to 150°. At a more moderate temperature (115°), the amino group remains in the molecule, and the products are hemipinic acid and 1-dimethylaminoethyl-2-cyan-3-methoxy-4,5-methylenedioxybenzene. The latter may be converted to the before-mentioned vinyl compound by heating its methiodide with alkali.

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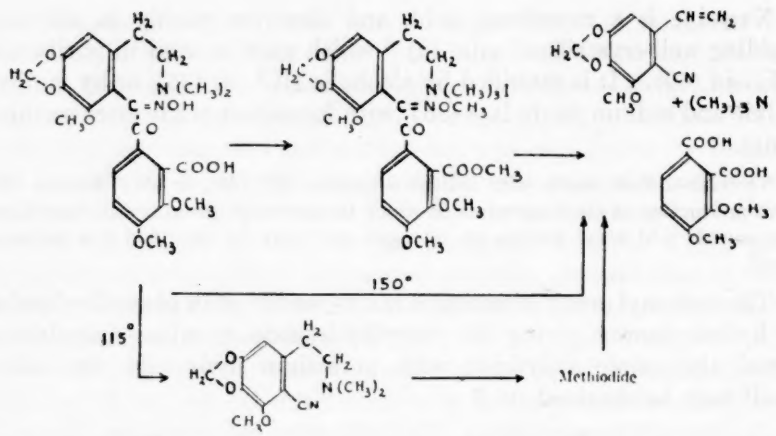
[66] Compare Anderson, Ann. **86**, 179 (1853).

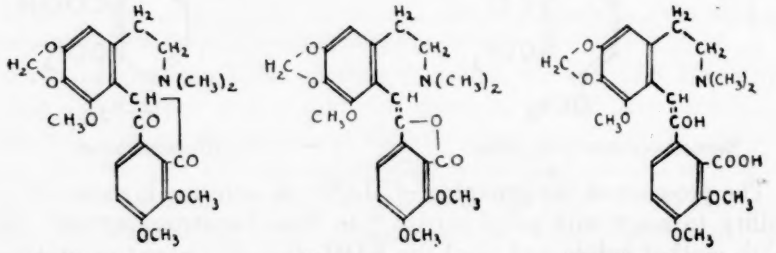
* See Appendix, p 358.

[67] Method of Claisen, Ber. **20**, 655 (1887); *cf.* Meyer and Oelkers, Ber, **21**, 1304 (1888).

[68] The cotarnone nitrile of Roser (37). By this compound, as well as by the products of decomposition of bromonarcindonine (q. v.) narceine is linked up with the substances resulting from the hydrolysis or oxidation of narcotine (cotarnine, hydrocotarnine, hemipinic acid).



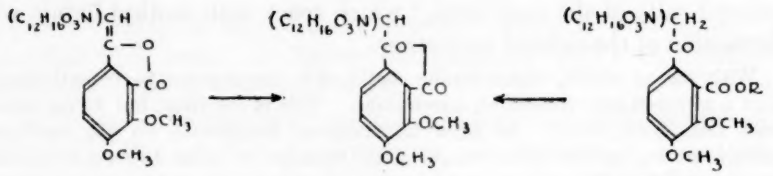
Of considerable importance for the development of the narceine formula were the researches which had their beginning in the preparation of aponarceine (lactonarceine) by Tambach and Jäger (38). This compound was obtained in an attempt to condense urethane with narceine by the action of phosphorous oxychloride, and was believed by these investigators to have the structure I.



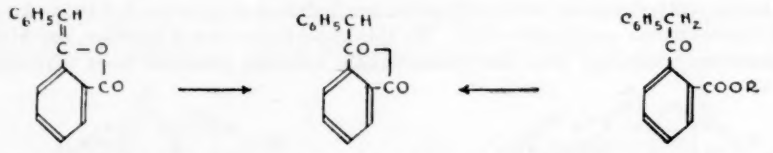
I. Narcindonine II. Aponarceine III. Hypothetical narceine-enol

Freund (39), however, objected that this structure could not account for the easy conversion back to narceine on boiling with alkali, and considered aponarceine to be a lactone of Formula II, derived by loss of water from the hypothetical enol form of narceine (III). In support of this, he advanced the rearrangement of aponarceine with sodium methylate into narcindonine (Formula I above), a derivative of phenylindanedione. This reaction is parallel to the rearrangement of benzylidene phthalide into phenylindanedione.[69] Moreover, just as the analogous desoxybenzoin carboxylic esters undergo a parallel change,[70] narceine ethyl ester may be converted directly to narcindonine by means of sodium methylate:

[69] Gabriel, Ber. **26**, 951, 2576 (1893); **37**, 3006 (1904).
[70] Eibner, Ber. **39**, 2202 (1906).

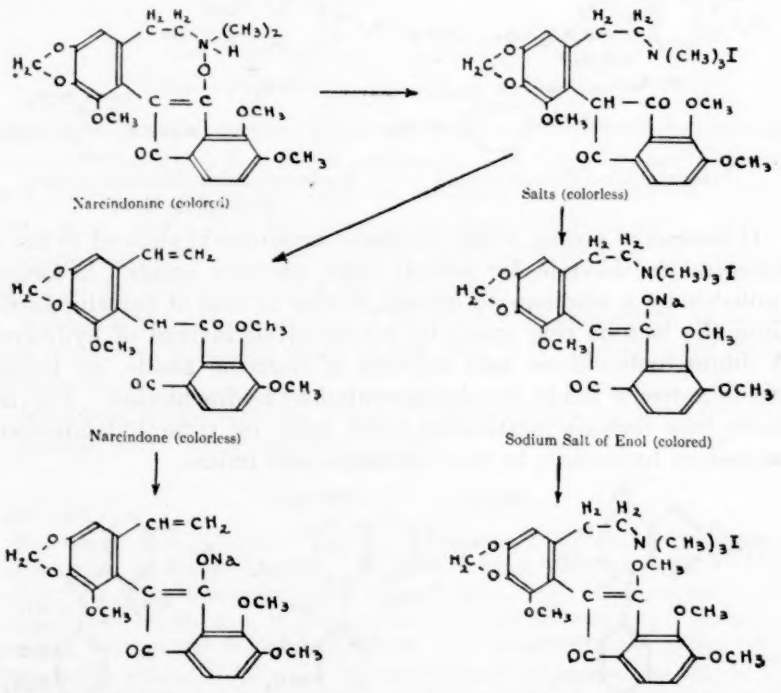


Narceine Narcindonine Narceine Ester



Benzylidene Phthalide Phenylindanedione Desoxybenzoin Carboxylic Ester

In analogy with the colored salts derived from the colorless phenylindanedione, narcindonine, which crystallizes in azobenzene-colored plates, is to be regarded as an inner salt of the hypothetical enol form (35):



Narcindonine (colored) Salts (colorless)

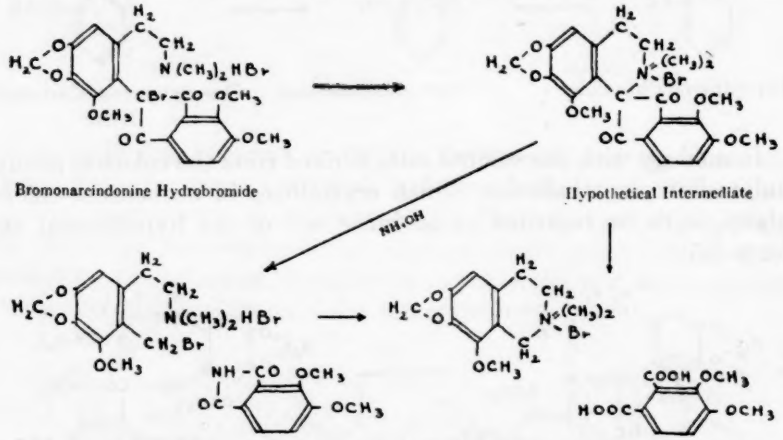
Narcindone (colorless) Sodium Salt of Enol (colored)

Narcindone Sodium (colored) Narcindonine Enol Ether (colored)

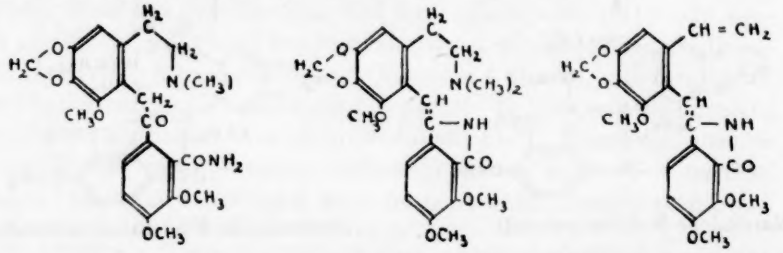
In agreement with this hypothesis, the salts of narcindonine with acids or alkyl halide are colorless. The latter dissolve in alkali to give

colored salts of the enol form,[71] which react with methyl iodide with formation of the colored enol ether.

With strong alkali, narcindonine methiodide decomposes to trimethylamine and a nitrogen-free substance, narcindone. This is colorless, but forms colored enol salts with alkali. As phenylindanedione brominates on the methylene carbon atom, narcindonine reacts with bromine to give bromonarcindonine hydrobromide. The brominated free base can not be isolated by treatment with alkali; in the moment of formation it decomposes to hemipinic acid and hydrocotarnine methobromide, which with potassium iodide may be converted to the known hydrocotarnine methiodide (35). By this important series of reaction, narceine is therefore connected with the characteristic splitting products from narcotine.



If instead of strong alkali, alcoholic ammonia is allowed to act on narcotine methiodide for several days, narceine amide[72] is formed, probably by a reaction-mechanism similar to that of narceine formation; the lactone ring opens by ammonolysis instead of hydrolysis. A dilute hydrochloric acid solution of narceine amide, on boiling, yields narceine imide (methylnarcotimide) hydrochloride. The free imide base forms a methiodide which splits off trimethylamine with potassium hydroxide, to give narceonic acid imide.

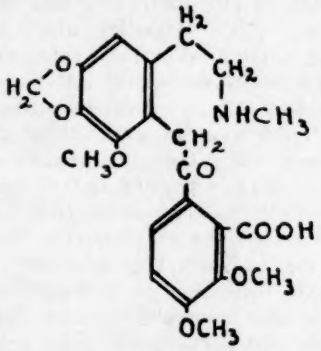


[71] Similar relationships exist, for example, in the case of dibenzoylacetylmethane, which in the keto form is colorless, but forms highly colored enol salts. (Michael, Ber. 39, 208 (1906); 40, 4380 (1907).)

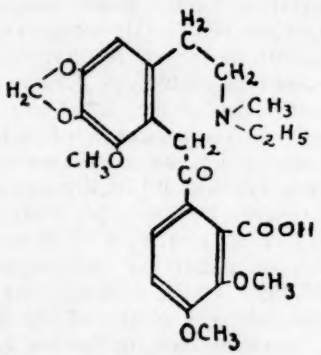
[72] The methylnarcotamide of Freund and Heim, D. R-P. 58394 (50).

Narceine imide is the primary product obtained from a melt of narceine with urea. At higher temperatures (200°) an indifferent substance of m. p. 194° results (8).

Nornarceine results from treatment of narcotine with dilute acetic acid. The first product of the reaction is gnoscopine (*d*, *l*-narcotine), whose nitrogen ring is then opened to form on the one hand nornarceine, on the other, cotarnine and meconin. The structure of nornarceine is evident from the smooth alkylation with sodium methylate and methyl iodide, to narceine methyl ester methiodide (36).



Nornarceine



Homonarceine

Like narceine, nornarceine forms an isonitroso derivative, which likewise undergoes the Beckmann rearrangement, forming hemipinic acid and 1-methylaminoethyl-2-cyan-3-methoxy-4,5-methylenedioxybenzene (41). Rabe (41) believes that nornarceine is identical with the alkaloid oxynarcotine; this identity has been disputed by Gadamer and von der Bruck (56) (see Oxynarcotine).

Homonarceine (6) is prepared by the action of sodium hydroxide and steam on narcotine ethochloride and is chemically very similar to narceine.

Dedimethoxynarceine is formed in the same manner from anhydrocotarnine phthalide methochloride (42).

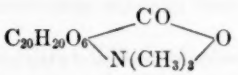
Descriptive Part (Narceine)

NARCEINE, B=$C_{23}H_{27}O_8N$. —HYDROCHLORIDE (9) Crystallizes with varying amounts of water (43) (44). Desiccator dried, $C_{23}H_{27}O_8N \cdot HCl + 5\frac{1}{2}H_2O$. At 120° it is obtained anhydrous, and melts at 188° to 192°. $C_{23}H_{27}O_8N \cdot HCl \cdot 3H_2O$ is also known (4) (6) (9). If prepared in methyl alcohol solution, it gives rhombohedra, 190° to 192° $B \cdot HCl + CH_3OH$, in ethyl alcohol, rhombic plates 158° to 159°, $B \cdot HCl + C_2H_5OH$ (9). Commercial narceine may contain as high as 14% hydrochloride (12). —NITRATE (9), pale yellow needles, decomposing at 97°, $B \cdot HNO_3 + H_2O$. —SULPHATE (9), dried, corresponds to the formula $B \cdot H_2SO_4$. *Cf.* Beckett and Wright (32), who found $C_{23}H_{29}O_9N \cdot H_2SO_4 + 10H_2O$. —METHYLSULPHURIC ACID, from heating narceine in alcohol with dimethyl sulphate, rhombic crystals (alcohol) fine needles (water), m. p. 200° to 201° (38). It is not narceinium sulphate as Tambach and Jäger believed, but has formula $B \cdot HSO_4$-

CH_3 (39). —MECONATE (45), lemon yellow crystals, sol. hot water, m. p. 126°. —PICRATE, from abs. alcohol m. p. 195° corr. (46). —PLATINICHLORIDE, $(B{\cdot}HCl)_2PtCl_4+2H_2O$, needles melting at 190° to 191°, decomposing at 195° to 196° (9); monoclinic prisms, water-free, m. p. 196° to 198° (6); m. p. 180° (3). —AURICHLORIDE, yellow-red needles from alcohol, m. p. 130° (6). —METHIODIDE, from narceine and methyl iodide at 100°. From water, asbestoslike needles, diff. sol. water, m. p. 207° (39). *Cf.* Claus and Ritzefeld (47).[73] —METHOCHLORIDE, white needles, sol. water, alcohol, m. p. 210° (47). Freund (39), in spite of the difference in m. p. claims, with good evidence, that the methylnarceine hydrochloride (m. p. 243°) of Tambach and Jäger (38) is identical with this; –Platinichloride, yellow crystalline powder, m. p. 189°; (47)–"Methylnarceine platinichloride," yellow leaflets, m. p. 209° to 210° (38). (See also under Methylnarceine.) —METHONITRATE, from water, white needles, which turn brown with time; m. p. 168° (47). —ETHIODIDE, obtained from the components in sealed tube at 100°. —ETHOHYDROXIDE, seems to decompose into narceine and ethyl alcohol (32) (*Cf.* Claus and Ritzefeld (47)). —ETHOBROMIDE, obtained from the components in sealed tube for 5 hours at 100°. Crystallizes from alcohol in white needles, water-soluble, m. p. 165°; –Cadmium bromide salt, colorless needles, $B{\cdot}C_2H_5Br{\cdot}CdBr_2(+H_2O$?) (47). —ETHOCHLORIDE, results from treatment of the ethobromide with silver chloride, crystallizes from water or alcohol, m. p. 170° (47). Freund (39) considers the ethylnarceine hydrochloride (m. p. 231°) of Tambach and Jäger (38) to be identical with this; –Platinichloride, is formed as a yellow precipitate (becoming crystalline) from a hydrochloric acid solution of the ethobromide with chloroplatinic acid. M. p. 170°, becoming dark; on heating further, evolves trimethylamine (47). –Mercurichloride, white crystalline precipitate, recrystallized from water, m. p. 127°. $B{\cdot}C_2H_5Cl{\cdot}HgCl_2+H_2O(2H_2O$?) (47). —ETHONITRATE, from the ethobromide with $AgNO_3$. Silky needles, water-soluble, m. p. 155° (47). —ETHOXALATE, from the ethobromide with silver oxalate. Colorless needles, decomposing at 174°; $(B{\cdot}C_2H_5)C_2O_4+6H_2O$ ($8H_2O$?) (47). —BENZOCHLORIDE, from refluxing narceine with benzyl chloride 6 hours; white needles from water or alcohol, m. p. 162°. With alkali it is said to give benzylnarceine (47). *Cf.* Freund and Frankforter (9); –Platinichloride, yellow crystalline powder, m. p. 165°, $(B{\cdot}C_7H_7Cl)_2PtCl_4$ ($+2H_2O$?). From conc. HCl solution an acid salt is obtained, $B{\cdot}C_7H_7Cl{\cdot}HCl{\cdot}PtCl_4(+H_2O$?) (47). —SILICOTUNGSTATE, from narceine with silicoduodecitungstic acid. Reddish crystals, $B_4{\cdot}(2H_2O{\cdot}SiO_2{\cdot}12WO_3)$ (48). —SESQUIIODIDE, from a dilute solution of narceine hydrochloride with KI_3; bronze-brown rectangular prisms, from which narceine may again be obtained, $(B{\cdot}HI)_2I$ (9) (54). —PERIODIDE, from treatment of the sesquiiodide with alcoholic iodine, long brown needles, $B{\cdot}HI_3$ (9) (54). —OTHER IODIDES (25), $B_3I_2+3H_2O$, from narceine with aqueous iodine, blue needles, 176° to 177° or 180° to 181°, sl. sol. in water, alcohol; converted to narceine by NaOH. B_3I+3H_2O, from narceine with alcoholic iodine, on heating changes to red form. With $AgNO_3$ gives hexagonal columns, m. p. 110° to 112°. POTASSIUM—, from narceine in 33% KOH, at 70°, soluble in water or alcohol. Separates from absolute alcohol on addition of ether in crystal rosettes, m. p. 90° (9) (60), $C_{23}H_{26}O_8NK{\cdot}C_2H_5OH$. SODIUM—, prepared in the same way as the potassium compound, white prisms, 159° to 160°, $C_{23}H_{26}O_8NNa{\cdot}C_2H_5OH$. It loses its crystal-alcohol on long standing with the alcohol-ether mother liquor. May be used to purify narceine (9) (60) (61). BARIUM—, precipitates in needles on addition of $BaCl_2$ to a solution of sodium narceine. Sp. sol. water, mod. sol. alcohol, m. p. 182° $(C_{23}H_{26}O_8N)_2Ba$. (9). SILVER—, from a solution of the sodium salt with silver nitrate; white powder,

[73] All analyses by Claus and Ritzefeld (47) correspond with the formula $C_{23}H_{29}O_9N$ for narceine. Many of these salts have not been subsequently analyzed.

easily decomposed (9). LEAD—, white needles, diff. sol. in water or alcohol, m. p. 157° (9). COPPER—, green powder, m. p. 172°, insol. in water or alcohol, decomp. by heating in these (9). —METHYL ESTER METHIODIDE, is formed by treatment of sodium narceine in methyl alcohol with methyl iodide; m. p. 208° to 209° (9) (39). Also from narceine or nornarceine with methyl iodide and sodium methylate (36). Identical with the supposed methylnarceine methiodide of Tambach and Jäger (38). The alcohol used as solvent takes no part in the alkylation. (*Cf.* Freund and Frankforter (9)). —ETHYL ESTER; -Hydrochloride, results from the action of boiling alcoholic HCl, white needles of m. p. 206° to 207°; -Platinichloride, m. p. 194° to 195°; -Hydrobromide, prisms, m. p. 215° to 216°; -Hydriodide, prisms, m. p. 212° (9); -Methiodide, 209° to 211° (38); -Ethiodide, from alcohol, m. p. 191° to 193° (38), m. p. 180° to 181°, holding 1 C_2H_5OH; from water m. p. 141°, holding 1 H_2O (39); -Ethochloride, the ethylnarceine ethyl ester hydrochloride of Tambach and Jäger (38), (Freund (39)) m. p. 218° to 219°, soluble in water or alkali; -Ethochloride platinichloride, m. p. 220°. —ALLYL ESTER ALLYL IODIDE, from sodium narceine and allyl iodide in ethyl alcohol. Powder, m. p. 154° to 155° (9) (39). —METHOHYDROXIDE BETAINE,



This formula is assigned by Freund (39) to the methylnarceine of Tambach and Jäger (38), obtained from action of alcoholic KOH on narceine ethochloride; m. p. 266° (decomp.), soluble in water, sparingly in alcohol, ether; -Sodium salt, leaflets, soluble water or alcohol. —ETHOHYDROXIDE BETAINE (39), the ethylnarceine of Tambach and Jäger (38). M. p. 175° to 177°.

METHYLNARCEINE: From boiling narceine methiodide with KOH, colorless needles, sl. sol. water, m. p. 175° (47). Freund and Frankforter (9) and Tambach and Jäger (38) were not able to repeat this preparation. Narceine-sodium with dimethyl sulphate (57) (59) gives METHYLNARCEINE; Hydrochloride, m. p. 242°; -Methomethylsulphate, 184° to 186°; -Ester hydrochloride, m. p. 214° to 216°, whose platinichloride m. 220°.

ETHYLNARCEINE (57) (59): HYDROCHLORIDE, m. p. 231°. —ETHIODIDE, 140° to 144°. —ETHYL ESTER HYDROCHLORIDE, m. p. 219°. —ETHYL ESTER METHIODIDE, 184° to 185°.

BENZYLNARCEINE: From the action of KOH on narceine benzochloride, white needles, 169°. —PLATINICHLORIDE, yellow crystalline precipitate, carrying $2H_2O$, m. p. 128° (47). Existence doubtful (see F. and F. (9) and T. and J. (38)).

NARCEINE OXIME (9): From heating the oxime anhydride with KOH. Prisms from alcohol, m. p. 167° (decomp.) $C_{23}H_{28}O_8N_2+H_2O$. Loses $2H_2O$ at 110° to give the anhydride. K salt, m. p. 155° to 156°. —ANHYDRIDE, from boiling narceine with aqueous hydroxylamine hydrochloride, white crystals from alcohol, m. p. 171° to 172°. —HYDROCHLORIDE, m. p. 206° to 208°.

NARCEINE PHENYLHYDRAZONE-ANHYDRIDE HYDROCHLORIDE (9): From boiling narceine 40 hours with aqueous phenylhydrazine hydrochloride. Out of water, m. p. 180° to 182°. Heated alone or in absolute alcohol it gives an isomeric salt in needles, m. p. 220°, probably due to the change

$$-CH_2-\underset{|}{C}=N- \rightleftarrows -CH=\underset{|}{C}-NH-$$

NARCEINE AMIDE (METHYLNARCOTAMIDE) (40) (50): From the action of cold alcoholic NH_3 on narcotine methiodide. Out of dilute alcohol, $C_{22}H_{28}O_7N_2+H_2O$, m. p. 125°, resolidifying, anhydrous m. p. 178°. —HYDROCHLORIDE, by treatment of the base with NH_4Cl solution, m. p. 236° to 237°.

NARCEINE IMIDE (METHYLNARCOTIMIDE) (40): From boiling a dilute HCl solution of narceine amide, the HYDROCHLORIDE precipitates crystalline, m. p. 239° to 240°. The free base is obtained from this with Na_2CO_3, yellow rods from dilute alcohol, m. p. 150°, $C_{23}H_{26}O_6N_2$. —NITRATE, from narceine amide treated with dil. HNO_3, m. p. 224° to 225°. —ACID SULPHATE, m. p. 194° to 195°. —METHIODIDE, yellow prisms, m. p. 244° to 245°. This yields on treatment with 50% KOH, narceonic acid imide.

NITRONARCEINE (55): From nitro-β-gnoscopine methiodide by successive action of AgCl, KOH and boiling water. Orange microcrystals, m. p. 160° to 170°. Gives no color with iodine. K-salt, yellow prisms.

APONARCEINE (38), (LACTONARCEINE (39), METHYLNARCOTINE (41)): Is formed by treatment of narceine with $POCl_3$ or other dehydrating agents (61), pale yellow crystals from alcohol, m. p. 112° to 115°, $C_{23}H_{25}O_7N$, sp. sol. water or alkali. On boiling with alkali, it is converted to narceine. —HYDROCHLORIDE, canary yellow, m. p. 144°, (m. p. 128° to 130° (41)) $B{\cdot}HCl+H_2O$ (38). Aponarceine also results from treatment of narcotine methochloride with dilute NaOH. It is unsaturated to bromine or $KMnO_4$, basic to litmus, optically inactive. In benzene with CH_3I it gives the methiodide, m. p. 260°; in methyl alcohol with CH_3I the lactone ring opens, and narceine methyl ester methiodide (m. p. 211°) is formed.

NARCINDONINE: From digestion of narceine ethyl ester hydrochloride in methyl alcohol with $NaOCH_3$ at 100°; separates from water as azobenzene-colored plates, m. p. 168° to 169°, $C_{23}H_{25}O_7N+1\frac{1}{2}\ H_2O$. Anhydrous, it melts at 174°. It is likewise produced by the action of $NaOCH_3$ on aponarceine (39). It forms colorless salts with acids or alkyl halides, colored salts with bases, and colored enol ethers. —HYDROCHLORIDE, white prisms, m. p. 255°. —HYDRIODIDE, from sodium salt in glacial acetic acid with KI, m. p. 246°. —METHIODIDE, microscopic white plates m. p. 217°, dissolves red in alkali. —METHYL ETHER METHIODIDE, from sodium salt with CH_3I at 100°, yellow-red plates from alcohol, m. p. 207°, insoluble in alkali. NARCINDONINE SODIUM, deep-red four-sided plates decomp. at 210° to 272°, $C_{23}H_{24}O_7NNa$.

BROMONARCINDONINE HYDROBROMIDE: From treatment of narcindonine sodium with Br_2 in acetic acid. White plates with $1\frac{1}{2}\ CH_3COOH$, m. p. 150° decomp. With alkali it yields des-N-methyl-hydrocotarnine, hydrocotarnine methobromide, and sodium hemipinate (35).

NARCINDONE: Results from treatment of narcindonine methiodide with $NaOC_2H_5$ at 100°; six-sided plates from gl. acetic acid, m. p. 136° to 137°, $C_{21}H_{18}O_7$ (35). It is nearly colorless, but dissolves in alkali with deep red color.

ISONITROSONARCEINE, $B=C_{23}H_{26}O_9N_2$ (35): From narceine and dilute $NaOC_2H_5$ with ethyl nitrite, 2 days at 0°. With gl. acetic acid, white plates, m. p. 178°, $B+C_2H_5OH$. Dissolves yellow in alkali, from which acetic acid separates white plates, m. p. 173°, $B+H_2O$. Boiling either compound in water gives the base containing no solvent, as prisms of m. p. 196°. —HYDROCHLORIDE, prisms m. p. 223°. —METHYL ETHER METHYL ESTER METHIODIDE, from base in alcoholic alkali with CH_3I, white needles out of water, m. p. 247°. Isonitrosonarceine at 115° gives hempinic acid and 1-dimethylaminoethyl-2-cyan-3-methoxy-4,5-methylenedioxybenzene, from ether m. p. 50°, insol. water, $C_{13}H_{16}O_3N_2$, hydrochloride, m. p. 204°, methiodide, decomp. 225° to 226°, converted by alkali to 1-vinyl-2-cyan-3-methoxy-4,5-methylenedioxybenzene (cotarnone nitrile), m. p. 156°.

NARCEONIC ACID, $C_{21}H_{20}O_8$ (9): From treatment of crude narceine methiodide with alkali, m. p. 217° (39). —SILVER SALT, white, decomp. 165° (40). —IMIDE, from narceine imide methiodide with 50% KOH, yellow needles from acetic acid, m. p. 177.5° to 178.5°. —PHENYLHYDRAZONE ANHYDRIDE, white

prisms from alcohol-acetic acid, m. p. 181° to 182°. —OXIME ANHYDRIDE, from gl. acetic acid, leaflets and needles, m. p. 201° to 202°. —MONOBROMIDE, from action of two atoms of bromine in gl. acetic acid, m. p. 171° to 172°. —TRIBROMIDE, from action of excess of bromine, m. p. 231° to 232° (40).

NORNARCEINE, B=$C_{22}H_{25}O_8N$: From refluxing narcotine 8 days with 50% alcohol (51); from heating narcotine with dilute acetic acid (36); see also the alkaloid, oxynarcotine. Optically inactive (41). B·$3H_2O$, m. p. 205° to 222° (decomp.), anhydrous m. p. 147° (decomp.). Heated in alcohol, gives a second solvent-free modification, m. p. 229° (decomp.). —HYDROCHLORIDE, B·HCl·H_2O, m. p. 144°. —HYDROBROMIDE (55), B·HBr·$2H_2O$, needles m. p. 128° to 131°.—OXIME ANHYDRIDE HYDROCHLORIDE, $C_{22}H_{24}O_7N_2$·HCl+C_2H_5OH, m. p. 138°. With Ag_2CO_3, it gives the oxime, m. p. 171°. Nornarceine with $NaOCH_3$ and CH_3I gives narceine methyl ester methiodide, m. p. 208° (36).

ISONITROSONORNARCEINE: From the action of dilute sodium ethylate and ethyl nitrite, 60 hours. From water, m. p. 167° to 169°. With PCl_5 it splits into hemipinic acid and 1-methylamino-2-cyano-3-methoxy-4, 5-methylenedioxybenzene, m. p. 61°. —HYDROCHLORIDE, decomp. 206° to 207°. —METHIODIDE, 226°, identical with the methiodide obtained by Freund and Oppenheim (35) from decomp. of isonitrosonarceine (41). —PICRATE, 168°. —PICRONOLATE, decomp. 232°.

BROMONORNARCEINE, $C_{11}H_{14}O_3N$·CHBr·CO·$C_6H_9O_4$ (55): From water, m. p. 198° to 200° (decomp.) insol. soda, sol. NaOH but precip. by CO_2. It gives a hydrobromide of m. p. 134° to 136°, a hydrochloride of m. p. 126° to 128°.

HOMONARCEINE, $C_{24}H_{29}O_8N$·$3H_2O$ (6): From narcotine ethochloride with NaOH and steam. Fine needles, m. p. 173° (decomp.), sol. in water, alcohol, alkalies (reprecipitated by CO_2). Loses 3 H_2O at 100°. —MERCURICHLORIDE, white needles. —PLATINICHLORIDE, yellow needles, $(C_{24}H_{29}O_3N·HCl)_2PtCl_4·2H_2O$. —METHOCHLORIDE, on the basis of the work of Freund (39), the methyl homonarceine hydrochloride of Tambach and Jäger (38) must be considered as homonarceine methochloride; prisms from dil. alcohol m. p. 230° to 231° (decomp.); forms a Platinichloride, m. p. 181° to 182°. —ETHYL ESTER METHOCHLORIDE, from alcohol, m. p. 212°; Platinichloride, m. p. 217° to 218°. This is the methyl homonarceine ethyl ester hydrochloride of Tambach and Jäger (38). —METHYL ESTER HYDROCHLORIDE, m. p. 134° to 135° (52). —ETHYL ESTER HYDROCHLOCHLORIDE, m. p. 168° to 169° (52). HOMONARCEINE AMIDE, from narcotine ethobromide with ammonia, m. p. 111° (50).

METHYLHOMONARCEINE (57): HYDROCHLORIDE, m. p. 231° to 232°. —PLATINICHLORIDE, 181° to 182°. —ETHYL ESTER HYDROCHLORIDE, m. p. 212° to 214°. ETHYLHOMONARCEINE HYDROCHLORIDE, m. p. 211°.

DEDIMETHOXYNARCEINE, $C_{21}H_{23}O_6N$ (42): From anhydrocotarnine-phthalide methiodide (see under cotarnine), similar to narceine formation. Colorless laminae, m. p. 189° to 190°, forms sodium salt. —HYDROCHLORIDE, needles, m. p. 172° to 174° (decomp.). —PLATINICHLORIDE, yellow needles, $(C_{21}H_{23}O_6N·HCl)_2PtCl_4$.

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HYDROCOTARNINE

The alkaloid hydrocotarnine was first reported by Hesse (1) (1872), who found it in the mother liquors from the Robinson-Gregory process of morphine extraction. It is not certain whether hydrocotarnine as such exists in poppy juice or opium, or whether it is formed from narcotine during the operations involved in separation.

Hesse observed its similarity to cotarnine, and suggested that the hydrolysis of narcotine might take place according to the equation:

$$\underset{\text{Narcotine}}{C_{22}H_{23}O_7N} + H_2O = \underset{\text{Hydrocotarnine}}{C_{12}H_{15}O_3N} + \underset{\text{Opianic Acid}}{C_{10}H_{10}O_5}$$

instead of giving cotarnine and meconin as claimed by Matthiessen and Foster. The work of Beckett and Wright (2) confirmed this view of Hesse.

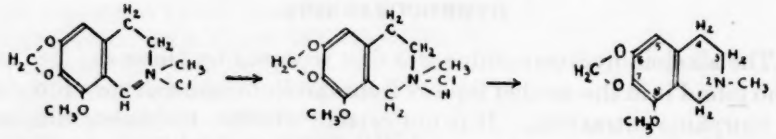
Hydrocotarnine is formed through hydrolysis of narcotine (2) or gnoscopine (*d*, *l*-narcotine) (3) by water at 140°, or more conveniently by the reduction of cotarnine with zinc and hydrochloric acid (2) with sodium amalgam and hydrochloric acid (4) or electrolytically (6).

The reduction with zinc is complicated by the formation of difficultly soluble zinc chloride double salts. (An 85% yield was, however, reported by Beckett and Wright.) The reduction with sodium amalgam (*cf.* Freund and Dormeyer (7)) gives a nearly quantitative yield of hydrocotarnine, approximately 3% of bis-hydrocotarnine being formed by dimolecular reduction. In the electrolytic method, one part of crude cotarnine was dissolved in 5.6 parts of dilute (1:5) sulphuric acid, and electrolyzed with a cathode current density of 3.5 amps. and a voltage of 5.3, using platinum electrodes. The end of the reduction was ascertained by testing a portion with ammonia until a pure white precipitate of m. p. 55° was obtained. Crude cotarnine gives directly pure hydrocotarnine, yield not stated.

Hydrocotarnine has also been obtained as a reduction product of methyl-N-methyltarconium iodide (8), or of didehydrocotarnine chloride (10).

Hydrocotarnine dissolves in conc. sulphuric acid with yellow color, becoming dirty red-violet on warming (1). In the "Magnol" test of David (11) an orange-red ring, shading to Alizarin yellow R in two hours is observed.

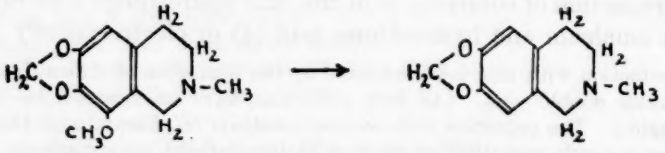
Pure hydrocotarnine crystallizes from light petroleum as colorless plates of m. p. 55.5° to 56.5° (4), soluble in alcohol, acetone, chloroform, benzene or ether. It is not appreciably soluble in water or alkali (1). The sparingly soluble hydrobromide is used for purification. Hydrocotarnine is optically inactive (9). Concerning absorption spectrum, see Steiner (12) (13) (14). It has the empirical formula $C_{12}H_{15}O_3N + \frac{1}{2}H_2O$; the water of crystallization is lost at 57° to 60° (1) (2). It may be distilled with little decomposition at 100° (15). The base is not affected by acetic anhydride and therefore contains no hydroxyl group (16). Hydrocotarnine is a tertiary base (16); its structure is evident from its method of formation, and from its oxidation to cotarnine by manganese dioxide or ferric chloride (2), or iodine (5) (8).



Cotarnine chloride — Hydrocotarnine Hydrochloride — Hydrocotarnine

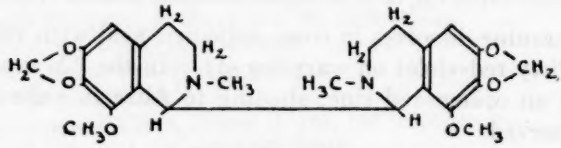
It is therefore 2-methyl-6, 7-methylenedioxy-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline.

Reduction of hydrocotarnine with sodium in alcohol leads to replacement of the methoxyl group by hydrogen, with formation of hydrohydrastinine. By this interesting reaction the opium alkaloids are linked up with those of *Hydrastis*. The methylenedioxyl group is also opened to a small extent in the reduction, to form phenolic bases (4) (5).



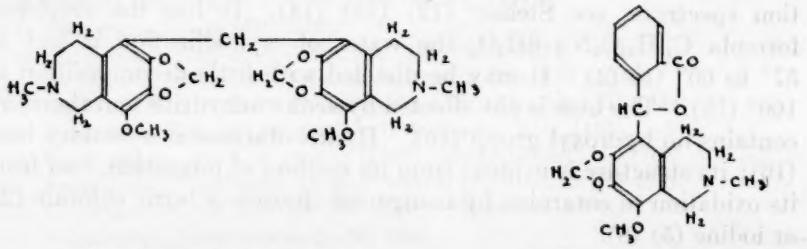
Hydrocotarnine — Hydrohydrastinine

The union of two hydrocotarnine molecules in the 1, 1-positions to bis-hydrocotarnine (dihydrocotarnine) takes place to some degree during reduction of cotarnine chloride with sodium amalgam (4), and by the action of the Grignard reagent (especially that from dihalogen compounds) on cotarnine (17) (18) (19). By the latter reaction an isomeric compound, iso-bis-hydrocotarnine is formed, but of the nature of the isomerism nothing is known.



Bis-hydrocotarnine

Hydrocotarnine undergoes numerous condensation reactions with aldehydes, as for example formaldehyde (20), and phthalaldehydic acid (21) (22) (23), condensation taking place on the 5-carbon atom:

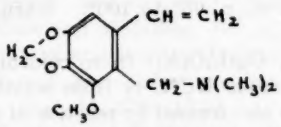


Methylene-di-hydrocotarnine — Hydrocotarnine Phthalide

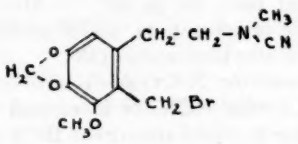
A similar condensation results in the formation of isonarcotine (21) (22) (see under narcotine). It should be noted that the reaction of cotarnine with substances containing an active hydrogen atom (25) or with the Grignard reagent (18) (24) leads to 1-substituted hydrocotarnine types (see also anhydrocotarnine derivatives).

It has been found that hydrocotarnines with groups other than benzyl (and its derivatives) or hydrogen in the 1-position are very resistant to oxidation to cotarnines (26).

The nitrogen ring of hydrocotarnine opens by exhaustive methylation, giving des-N-methylhydrocotarnine (27). The ring is also split by cyanogen bromide to a cyan-ethyl-amino-benzyl bromide derivative (28). Ethylchlorocarbonate also causes scission of the nitrogen ring (5).



Des-N-methylhydrocotarnine



Product from CNBr

The formation of hydrocotarnine methobromide by closure of the N-ring from narceine derivatives (27) is described under Narceine.

Descriptive Part (Hydrocotarnine)

HYDROCOTARNINE (B=$C_{12}H_{15}O_3N$), HYDROCHLORIDE: B·HCl·H_2O, white prisms very soluble in water (1) (2). —HYDROBROMIDE, B·HBr, less soluble than the hydrochloride, m. p. 236° to 237° (4) (29). —HYDRIODIDE, yellow prisms soluble in hot water (1). Colorless needles from methyl alcohol, m. p. 195° to 196° (30). —PICRATE, sol. with difficulty in cold water (1). —PLATINICHLORIDE, orange needles from conc. HCl, sinter 195° dec. 200°. —AURICHLORIDE and MERCURICHLORIDE (1) are known. —METHIODIDE, white needles from water, plates from alcohol, m. p. 206° (27) (30). —ETHIODIDE, white plates (16). —ETHOCHLORIDE, feathery crystals m. p. 100°, yields a Platinichloride (16). —METHOBROMIDE, white needles from $CHCl_3$, decomp. 221° (27).

1-ALKYLHYDROCOTARNINES: 1-METHYL—, $C_{13}H_{17}O_3N$, is formed by the action of methyl magnesium iodide on cotarnine (17) (18) (24). The free base is a viscous oil, but forms the crystalline Hydriodide, m. p. 178° to 180°; -Hydrobromide, m. p. 199° to 200°; -Acid sulphate, m. p. 155°; -Platinichloride, m. p. 220°; -Methiodide, m. p. 228° to 229°; -Amine oxide platinichloride, 198°; -Amine oxide hydriodide, 116°. 1-ETHYL— (18), $C_{14}H_{19}O_3N$, obtained from dil. alc. as rhombic double pyramids, m. p. 59° to 60°; -Hydrochloride, needles, m. p. 215° to 216°; -Dichromate, rhombic plates; -Methiodide, m. p. 188° to 189°; -Amine oxide platinichloride, quadrat. plates, m. p. 196° to 197°. 1-PROPYL— (18), $C_{15}H_{21}O_3N$, 4-sided prisms from ligroin, m. p. 66° to 67°; -Hydriodide, m. p. 165° to 166°; -Hydrobromide not crystalline; -Methiodide, m. p. 165° to 166°. 1-ISOPROPYL— (18), not crystalline; -Hydriodide, rhombic plates from alcohol, m. p. 196° to 197°; -Methiodide, needles m. 144° to 145°. 1-ISOBUTYL—, prisms m. 46° to 47° from ligroin; -Hydrochloride, m. p. 217° to 218°; -Hydrobromide, m. p. 205° to 206°; -Methiodide, m. p. 189° to 190°; -Platinichloride, 208° to 209°: 1-PHENYL—, prisms from ligroin or 50% alcohol, m. p. 97° to 98°.

1-ANISYL—, is not crystalline. 1-NAPHTHYL—, from alcohol, m. p. 120° to 122°; -Hydrobromide, m. p. 253°. 1-BENZYL—, rhombic plates from ligroin, m. 70°; -Hydriodide, m. p. 217° to 218° (17) (*Cf.* Pyman, (26) Salway (31).)

1-METHOXYHYDROCOTARNINE is obtained as the methiodide from treatment of cotarnine with methyl alcohol and methyl iodide, (methyl iodide alone gives only cotarnine methine methiodide); yellow needles from water, decomp. 173°: —METHOCHLORIDE not crystalline, but gives a PLATINICHLORIDE crystallizing in right-angled dendritic form. The free methoxy-base is not obtainable (*cf.* ethoxy-derivative) (32). 1-ETHOXYHYDROCOTARNINE is formed by treatment of cotarnine in the cold with absolute alcohol and concentration in vacuum. Prisms of m. p. 85°, decomp. 125°, decomp. slowly to cotarnine in air or with water (25); -Methiodide, pointed leaflets decomp. 168° (25) (32). ISOBUTOXYHYDROCOTARNINE METHIODIDE, leaflets m. p. ca. 120° (32).

1-ETHYLMERCAPTOHYDROCOTARNINE, $C_{14}H_{19}O_3NS$: From cotarnine in absol. ether with ethylmercaptan. Yellow-white crystals insol. in water, sensitive to acid and heat, m. p. 55°. —METHIODIDE, crystallizes from water with one molecule of solvent, m. p. 75° to 80°, anhydr. m. p. 95° to 100°. Warm HCl splits off ethylmercaptan (25).

1-CYANO-(or N-CYANO-?) HYDROCOTARNINE, $C_{13}H_{14}O_3N_2$: from cotarnine in dil. HCl with KCN, or in alcohol with anhydrous HCN, or from solution of cotarnine in liquid anhydrous HCN (33). It is also formed by reaction of cotarnine and mandelonitrile (34). Crystallizes from alcohol in prisms m. p. 95° to 96°. First named PSEUDOCOTARNINE CYANIDE by Hantzsch and Kalb (35). Concerning its structure see the theoretical discussion under Cotarnine. —METHIODIDE, crystals from hot water decomp. 204° to 205°. With alkali gives the carbonamide methiodide (m. p. 235°) (25). From anhydrous media cyanohydrocotarnine yields an unstable hydrochloride (33).

HYDROCOTARNINE CARBONAMIDE (1-amido-hydrocotarnine) is obtained as the methiodide from treatment of cyanohydrocotarnine with 10% aqueous sodium hydroxide; leaflets from dil. alcohol, m. p. 235°. Action of strong alkali on this opens the N-ring, giving 1-vinyl-3,4-methylenedioxy-5-methoxy-6-(dimethylamino-amido-methyl) benzene, m. p. 182°, numerous salts described. Vigorous treatment of this with HCl and KI give des-N-methylhydrocotarnine hydriodide (25).

HYDROCOTARNINE THIOCARBONAMIDE is obtained as the methiodide from boiling cyanohydrocotarnine methiodide with ammonium sulphide. Crystallizes from water in yellow prisms or needles, m. p. 203°. It suffers ring opening like the carbonamide with conc. alkali. —METHOHYDROXIDE, crystalline leaflets, m. p. 135°, containing 2 H_2O; m. p. anhydrous 141° to 142° (25).

HYDROCOTARNINE-5-PHTHALIDE: From reaction of phthalaldehydic acid and hydrocotarnine in 73% H_2SO_4. From alcohol, m. p. 193°; crystalline Hydriodide (21). Has structure analogous to that of isonarcotine (22).

3-NITRO-α-HYDROXYBENZYLHYDROCOTARNINE: (23) m. p. 170° to 171°. DI-(α-2-DIHYDROXYBENZYL) DI-HYDROCOTARNINE, amorphous. BENZYLIDENE-DI-HYDROCOTARNINE, m. p. 229° to 230°. PIPERONAL-DI-HYDROCOTARNINE, amorphous, m. p. 202°. CINNAMYLIDENEHYDROCOTARNINE, amorphous, dec. 228° to 230° (23). HYDROXYBENZYLHYDROCOTARNINE, from benzaldehyde and hydrocotarnine, from dil. alc., m. p. 240° (decomp.) (37).

5-BROMOHYDROCOTARNINE (29): m. p. 76°, Hydrobromide, Platinichloride; the so-called tribromohydrocotarnine hydrobromide is probably bromocotarnine hydrobromide superbromide.

BIHYDROCOTARNINE (19) (Dihydrocotarnine (17), bis-hydrocotarnine (4)), $(C_{12}H_{14}O_3N)_2$; from dihalogen organomagnesium compounds on cotarnine; rhombohedra from alcohol, m. p. 163° to 164°. —DIHYDROBROMIDE, m. p. 228°

to 229°. —DIHYDROCHLORIDE, leaflets m. p. 231° to 232°. —DIHYDRIODIDE, m. p. 228° to 230°. —MONOMETHIODIDE, m. p. 233° to 234°; for other salts see original (19). DIBROMO —, m. p. 178°; —Dihydrobromide, 233° to 234°. ISO-BIHYDROCOTARNINE, a stereoisomer, is identical with bihydrocotarnine in physical properties, excepting solubility.

METHYLENEDIHYDROCOTARNINE (20) (36) $C_{12}H_{14}O_3N$–CH_2–$C_{12}H_{14}O_3N$: From condensation of formaldehyde and cotarnine in presence of sulphuric acid; m. p. 211° to 212°. —DIHYDROBROMIDE, leaflets, 240° to 244°. —DIHYDRIODIDE, needles, m. p. 242°. —DIMETHIODIDE, yellow needles, m. p. 267°.

DES-N-METHYLHYDROCOTARNINE (27), (Hydrocotarninemethine): From the action of alkali on hydrocotarnine methobromide, is an oil, giving a METHOBROMIDE of m. p. 193°. —HYDRIODIDE (25), m. p. 229° to 230°.

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CRYPTOPINE

The alkaloid cryptopine, $C_{21}H_{23}O_5N$, was first isolated in the factory of T. and H. Smith, Edinburgh, by Smiles, in 1867. The name is said to be derived from the Greek kryptos, a cellar, as the base was found crystallizing from mother liquors stored below ground.* T. and H. Smith (1) (2) describe the separation of cryptopine as the hydrochloride, after the precipitation of morphine and thebaine; in this original preparation, only 5 ounces of the hydrochloride was obtained from about 5 tons of opium. A method of separating pure cryptopine was worked out by Hesse (3).

Morphine and codeine were precipitated by the Robinson-Gregory precedure, and the thebaine group thrown out with ammonia. The mother liquors were extracted with ether, and the alkaloid was shaken out from this with dilute acetic acid. Sodium hydroxide precipitated the bulk of the cryptopine, which was then dissolved in alcohol, acidified with acetic acid, and the solution diluted to precipitate papaverine and narcotine. The cryptopine was then precipitated as the hydrochloride (3).

Cryptopine is difficult to separate completely from the other rarer alkaloids occurring in opium. Gulland and Robinson (4) reported cryptopine in commercial thebaine. Many of the color reactions attributed to papaverine were shown (5) to be due to the presence of traces of cryptopine.

Cryptopine is probably present in opium in considerably larger amounts than the 0.003% observed by T. and H. Smith (1). Watt (6) estimated about 0.3% in Indian opium and Kauder (7) obtained about 3 pounds of crude cryptopine hydrochloride from 5,000 pounds of opium.

Cryptopine is best purified through the oxalate (8). The base crystallizes from alcohol, benzene, or petroleum ether as six-sided prisms or plates (5) (9); it may also be crystallized from methyl ethyl ketone, isoamyl alcohol, acetophenone, pyridine, or an alcohol-pyridine mixture (9); it is soluble in chloroform or acetic acid, sparingly soluble in alcohol (cold, 1 part in 455, hot, 1 part in 80 (5)).

Pure cryptopine melts at 217° to 218° (3) (9). It is optically inactive (9) (10), and attempts to resolve it have failed (9). Its density is 1.351 (11). The absorption spectrum resembles that of protopine and the spectra of the isoquinoline alkaloids (12) (13). The microchemical reactions of cryptopine were studied by v. Itallie (14). The following color reactions have been reported:

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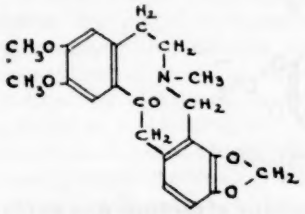
* See Appendix, p. 358.

Cryptopine: Color reactions

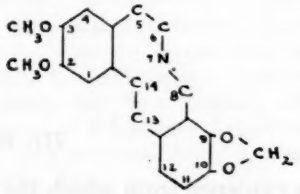
Reagent	Reaction	Observer
Basic magnesium hypochlorite.	Violet ring when layered onto solution of base in conc. H_2SO_4.	David (15).
Acetic-sulphuric acids	Pink → blue-violet → yellow lilac → dark green.	Perkin (9). David (15).
Conc. H_2SO_4	Dark blue-violet turning green then yellow	Pictet and Kramers (5).
H_2SO_4+H_3AsO_4	do	Do. (5).
Erdmann's reagent	Violet-rose turning gray then yellow	Do. (5).
Fröhde's reagent	Violet turning green then yellow	Do. (5).
Mandelin's reagent	Brilliant green turning yellow	Do. (5).
Labat's reagent	Green.	Do. (5).
Lafon's reagent	Green-blue turning brown	Do. (5).
Marquis' reagent	Violet turning brown	Do. (5).

Cryptopine is physiologically active, and has been studied in this connection by Munk (16), V. Schroeder (17), and others (18) (19) (20).

Hesse (3) in 1872 analyzed cryptopine and a number of its salts. The Hesse formula, $C_{21}H_{23}O_5N$, was confirmed by Brown and Perkin (8); Cook's (2) analyses were evidently carried out on impure material. The structural formula shown below was proposed for cryptopine by Perkin (9) in 1916.



I. Cryptopine



II. Numbering System [74]

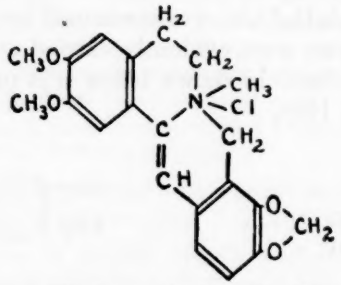
Cryptopine is more or less closely related to certain other natural bases. Allocryptopine (β-homochelidonine) differs from it only in that the methylenedioxyl and methoxyl groups occupy the reversed positions. The widely spread alkaloid protopine (p. 124) has the same structural skeleton as cryptopine, with a second methylenedioxyl group in place of the two methoxyls. Corycavine, from *Corydalis cava*, is a methylprotopine and also related to cryptopine. Berberine, and hydrastine more remotely, are of the cryptopine type.

The presence of two methoxyl groups in cryptopine was shown by Brown and Perkin (8) (9), and their location relative to the alicyclic portion of the molecule was established by the isolation of m-hemipinic acid (p. 7) from oxidative degradation (8). The formation of methylpiperonal (9) in oxidations of the cryptopine derivatives showed that a second aromatic nucleus carrying a methylenedioxyl group (5) must

[74] The numbering system used here for cryptopine is taken from that proposed by Buck, Perkin, and Stevens, J. Chem. Soc. 127, 1462 (1925) for the berberine series. The cryptopine formula of Perkin has been inverted, in accordance with present usage, to show more clearly its relationship to hydrastine, narcotine, etc., as they are generally formulated.

be in the cryptopine molecule. This accounts for four of the cryptopine oxygen atoms; the fifth is not in the form of a hydroxyl group (5), and is probably a carbonyl oxygen, despite the fact that it yields no oxime (9) (21). It can be reduced to a secondary alcoholic group, which readily undergoes dehydration (9) (21). The nitrogen atom of cryptopine is tertiary, and carries a methyl group (5).

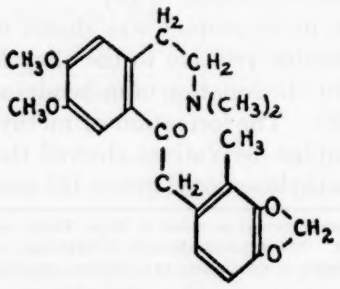
The conception of the remarkable 10-membered heterocyclic ring structure which links the two aromatic nuclei in cryptopine was developed mainly in the investigations of Perkin (9) (22). An analogous arrangement is found in the derivatives of berberine, as was shown by Pyman (23) and Freund (24). The 10-membered ring is capable of internal condensation, forming a new bond by which the large ring is divided into two 6-membered rings having the nitrogen and one carbon atom in common.



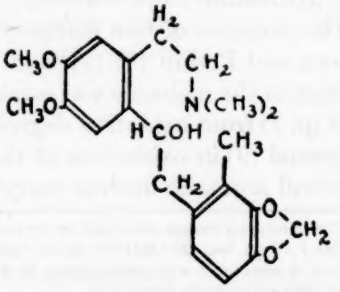
III. Isocryptopine Chloride

The evidence from which the above cryptopine structure was evolved will be outlined in the following paragraphs. The synthesis of cryptopine by Haworth and Perkin (25) (see below) confirms to a certain extent the Perkin structure.

Degradation of cryptopine methochloride or methomethylsulphate by the Emde method proceeds with scission of the nitrogen ring and reduction, giving dihydromethylcryptopine (IV), in which the carbonyl group may be reduced, with formation of tetrahydromethylcryptopine (V).

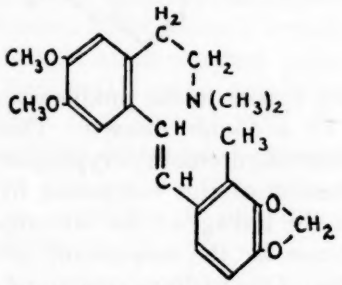


IV. Dihydromethylcryptopine

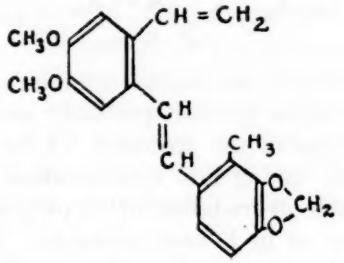


V. Tetrahydromethylcryptopine

Tetrahydromethylcryptopine, which may also be obtained directly by reduction of cryptopine methomethylsulphate, loses water in the presence of acetyl chloride, giving the stilbene derivative, anhydrotetrahydromethylcryptopine (VI). The normal Hofmann degradation of VI results in formation of the nitrogen-free cryptopidene (VII).



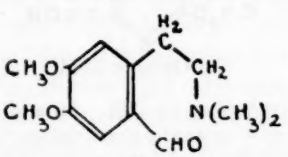
VI. Anhydrotetrahydromethylcryptopine



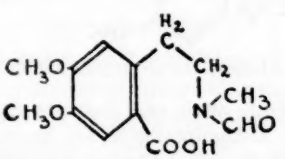
VII. Cryptopidene

Cryptopidene contains two double linkages, and reduces with sodium and alcohol to tetrahydrocryptopidene (9) (22).

The oxidation products from anhydrotetrahydromethylcryptopine and cryptopidene have played an important part in structure determination. Oxidation of the former with potassium permanganate (9) yields five products. Three of them are derived from the dimethoxylated nucleus, namely, m-hemipinic acid, 4, 5-dimethoxy-2-β-dimethylaminoethylbenzaldehyde, VIII (whose methiodide was found to be identical with the N-methyl-methiodide from Pyman's (26) 4, 5-dimethoxy-2-β-methylaminoethylbenzaldehyde), and N-formyl-4, 5-dimethoxy-2-β-methylaminoethylbenzoic acid (IX), which could be identified by conversion to dimethoxy-N-methyltetrahydroisoquinoline (26).

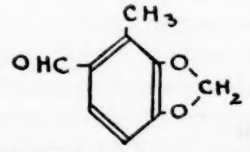


VIII

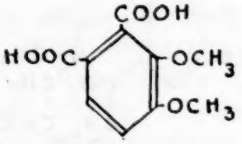


IX

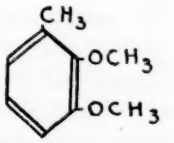
The remaining two oxidation products, methylpiperonal and methylpiperonylic acid contain the methylenedioxyl group. They were identified by converting the methylenedioxyl to two methoxyl groups (method of Barger (27)) and oxidizing to hemipinic acid. The position of the methyl group could be shown by the relationship to isohomocatechol dimethyl ether.



Methylpiperonal



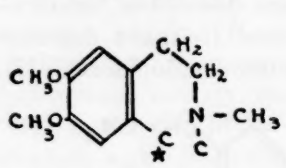
Hemipinic Acid

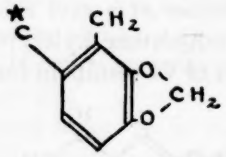


Isohomocatechol Dimethyl Ether

Oxidation carried out on cryptopine itself yielded only a derivative of the dimethoxylated aromatic ring, m-hemipinic acid.

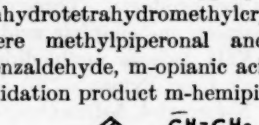
It is evident from these oxidation products that in anhydrotetrahydromethylcryptopine the two systems present are



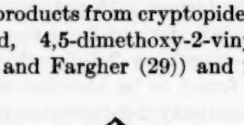


in which the starred carbon atoms, which appear in the products as aldehyde groups, probably are joined by a double linkage. This results in the structure VI for anhydrotetrahydromethylcryptopine and, taking into consideration the formation of this compound by Emde degradation of cryptopine, makes the linkage of the nitrogen ring as in I most probable. The evidence for the location of the carbonyl group depends upon the properties of the hydroxy compound, dihydrocryptopine, upon the formation and properties of the methylcryptopines, which can only be explained by the assumption of the carbonyl at position 14, and upon the relationships to the berberine series (28).

The oxidation of cryptopidene (VII) confirmed the structure derived from the anhydrotetrahydromethylcryptopine oxidation. The products from cryptopidene were methylpiperonal and methylpiperonylic acid, 4,5-dimethoxy-2-vinylbenzaldehyde, m-opianic acid (synthesized by Perkin and Fargher (29)) and its oxidation product m-hemipinic acid.



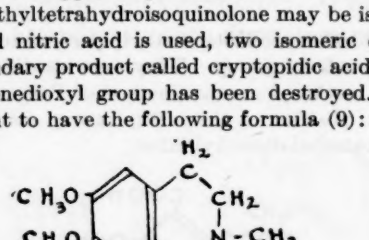
4, 5-Dimethoxy-2-vinylbenzaldehyde



m-Opianic Acid

Dilute nitric acid converts cryptopine into nitrocryptopine (9) (30). In addition, m-hemipinimide, the known (31) 3, 4-dimethoxy-6-methylcarbamylphenylglyoxylic acid, and what is apparently the mononitro derivative of the known (32) 6, 7-dimethoxy-N-methyltetrahydroisoquinolone may be isolated.

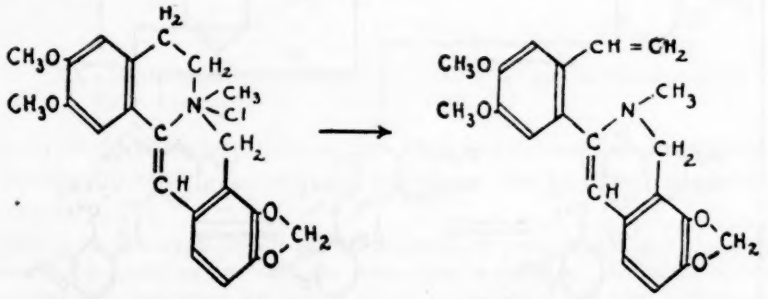
When concentrated nitric acid is used, two isomeric dinitrocryptopines are obtained, and a secondary product called cryptopidic acid, in which the nucleus carrying the methylenedioxyl group has been destroyed. Cryptopidic acid is dibasic, and is thought to have the following formula (9):



X. Cryptopidic Acid

Berberine and corydaline behave in a similar manner (33) (34).

Cryptopine forms a normal hydrochloride with cold hydrochloric acid. When heated with hydrochloric acid, or better, with phosphorous oxychloride or acetyl chloride, it undergoes internal condensation between the enol form of the carbonyl group and nitrogen. The enolic hydroxyl or chlorine which replaces it migrates to nitrogen, and a carbon to nitrogen linkage is set up which results in a double, hydrogenated isoquinoline ring system with a quaternary nitrogen atom common to both rings. The product, isocryptopine chloride (III), can not be converted back to cryptopine directly. When it is treated with alkali, one carbon-nitrogen bond breaks, resulting in anhydrocryptopine (XI), which contains an isoquinoline ring and a vinyl group in place of the condensed ring system. The reactions of anhydrocryptopine are considered in a later paragraph.



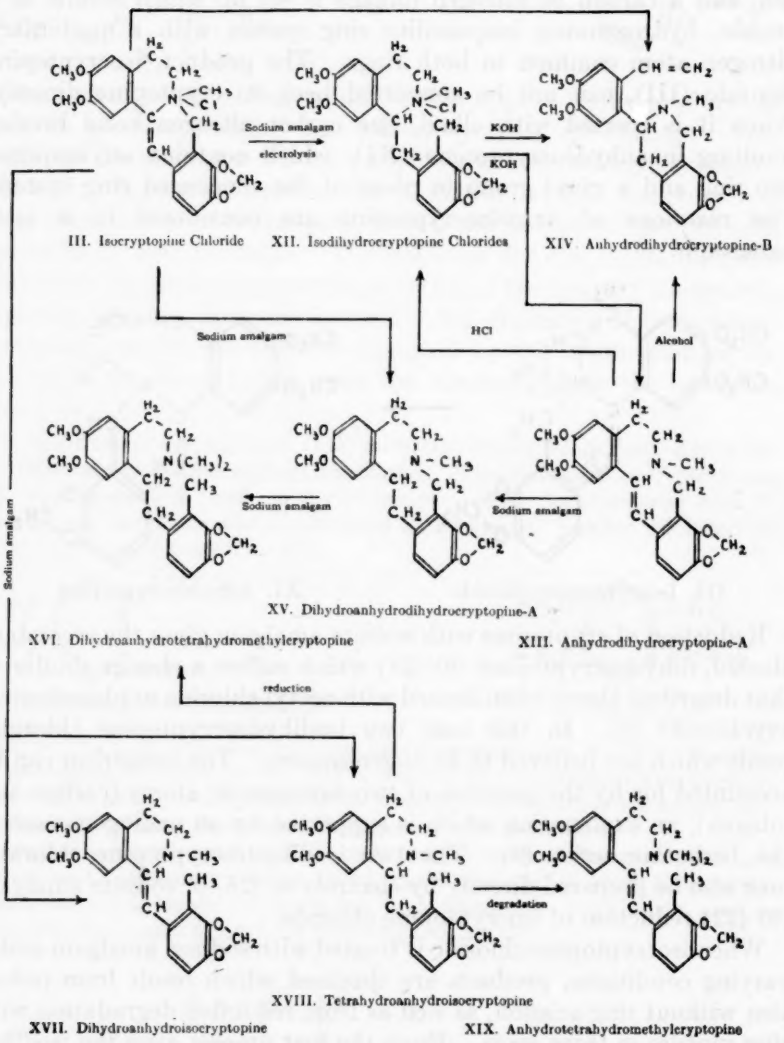
III. Isocryptopine chloride XI. Anhydrocryptopine

Reduction of cryptopine with sodium amalgam gives the secondary alcohol, dihydrocryptopine (9) (21) which suffers a change similar to that described above when heated with acetyl chloride or phosphorous oxychloride (9). In this case two isodihydrocryptopine chlorides result which are believed to be stereoisomers. The isomerism can be accounted for by the presence of two asymmetric atoms (carbon and nitogen), an explanation which is supported by an analogous case in the berberine series (9). The two isodihydrocryptopine chlorides may also be prepared directly by electrolytic (25) or sodium amalgam (9) (22) reduction of isocryptopine chloride.

When isocryptopine chloride is treated with sodium amalgam under varying conditions, products are obtained which result from reduction without ring scission, as well as from reductive degradation with ring rupture in three ways. From the first process arise the isodihydrocryptopine chlorides (XII) (synthesis, p. 113), from the second, anhydrodihydrocryptopine-B (XIV), dihydroanhydrodihydrocryptopine-A (XV) in which the 10-membered ring has been regenerated, and dihydro- and tetrahydro- anhydroisocryptopines (XVII and XVIII). The formulas assigned to the last two substances, with the 7,

8-bond broken, are confirmed by oxidation experiments and are in accord with the course taken by further degradations. The changes mentioned above were interpreted by Perkin as shown in the formulas of Plate I.

Plate I (To Cryptopine.)



III. Isocryptopine Chloride

XII. Isodihydrocryptopine Chlorides

XIV. Anhydrodihydrocryptopine-B

XV. Dihydroanhydrodihydrocryptopine-A

XVI. Dihydroanhydrotetrahydromethylcryptopine

XIII. Anhydrodihydrocryptopine-A

XVIII. Tetrahydroanhydroisocryptopine

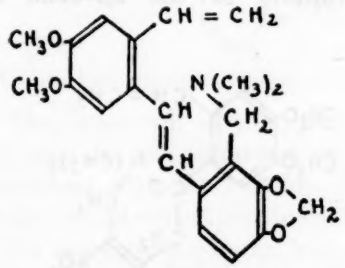
XVII. Dihydroanhydroisocryptopine

XIX. Anhydrotetrahydromethylcryptopine

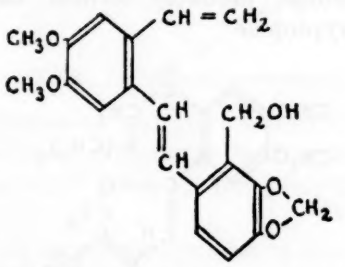
Whereas isocryptopine chloride gives only one product (anhydrocryptopine) on heating with alkali, isodihydrocryptopine chloride degrades in two ways, yielding by rupture of the 7, 14-linkage anhydrodihydrocryptopine-A, XIII (10-membered ring), or by breaking the 6, 7-linkage, the vinyl compound anhydrodihydrocryptopine-B XIV (Plate I). Anhydrodihydrocryptopine-A can be converted back

to isodihydrocryptopine chloride by digesting with hydrochloric acid or to its structural isomer anhydrodihydrocryptopine-B by boiling with alcohol.

The methomethylsulphates of the structural isomers anhydrodihydrocryptopine-A and -B degrade with alkali to one substance, methylisoanhydrodihydrocryptopine (XX), which on further exhaustive methylation gives the nitrogen-free α- and β-isocryptopidols (XXI).



XX. Methylisoanhydrodihydrocryptopine



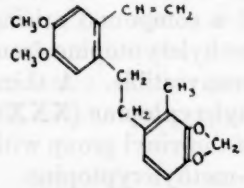
XXI. α- and β-Isocryptopidol

Anhydrodihydrocryptopine-A has been synthesized and converted to isodihydrocryptopine and to cryptopine itself. (See cryptopine synthesis, p. 113.)

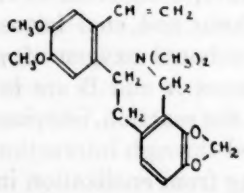
Anhydrodihydrocryptopine-B can be prepared by reduction of anhydrocryptopine, the degradation product from isocryptopine chloride. Anhydrodihydrocryptopine-B is converted by boiling dilute hydrochloric acid into hydroxyanhydrotetrahydrocryptopine, apparently through addition of the elements of water to the vinyl group (22).

Anhydrodihydrocryptopine-A is represented as containing an unsaturated 10-membered ring. The double linkage is reduced by sodium amalgam, giving the dihydroanhydrodihydrocryptopine-A (XV) mentioned above. In this the nitrogen ring may be opened by the action of sodium amalgam on the methomethylsulphate. The product, dihydroanhydrotetrahydromethylcryptopine (XVI) on further degradation goes to dihydrocryptopidene (XXII). Compound XVI has also been obtained by sodium amalgam reduction of isocryptopine chloride to tetrahydroanhydroisocryptopine (XVIII) and further reductive degradation of the methomethylsulphate of this substance.

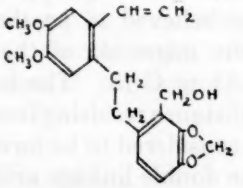
Dihydroanhydrodihydrocryptopine-A can be degraded through its methomethylsulphate by the Hofmann method to a vinyl derivative, dihydroisoanhydrodihydromethylcryptopine (XXIII) which can be further broken down to dihydro-α-isocryptopidol (XXIV).



XXII. Dihydrocryptopidene

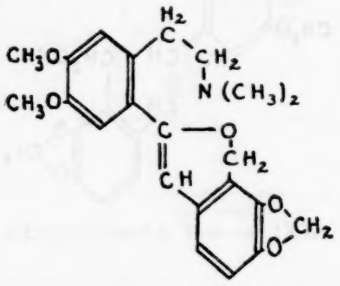


XXIII. Dihydroisoanhydrodihydromethylcryptopine

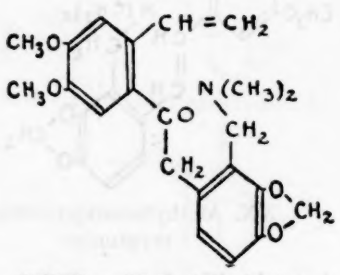


XXIV. Dihydro-α-isocryptopidol

METHYLCRYPTOPINES: (9) Exhaustive methylation of cryptopine results in scission of the 10-membered ring with formation of three isomeric methylcryptopines. α- and β-methylcryptopine are apparently polymorphic modifications of the same substance, and are interconvertible. γ-Methylcryptopine is a structural isomer. The β- isomer is not a ketone, and seems to be formed through opening of the 7, 8-linkage of cryptopine. γ-Methylcryptopine is a vinyl ketone, probably formed through rupture of the 6,7-bond in cryptopine.

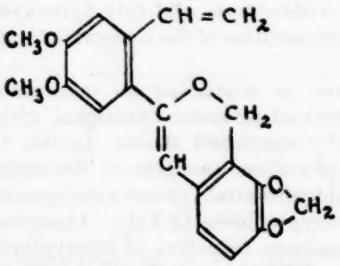


XXV. α-and β-Methylcryptopines

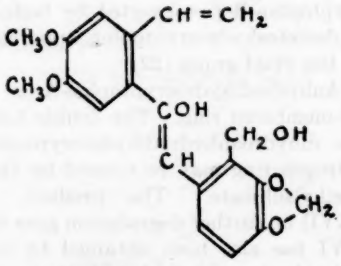


XXVI. γ-Methylcryptopine

The β- and γ-isomers, on further degradation are converted to the same nitrogen-free substances, anhydrocryptopidiol and cryptopidiol (XXVII and XXVIII).

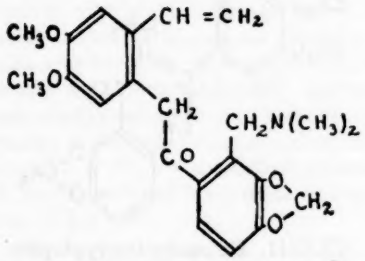


XXVII. Anhydrocryptopidiol

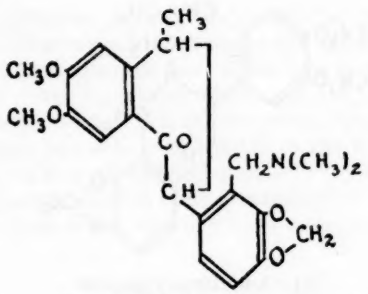


XXVIII. Cryptopidiol

γ-Methylcryptopine can be oxidized to a lactone corresponding to a m-homoopianic acid. Treatment of γ-methylcryptopine with concentrated hydrochloric acid results in the formation of two isomeric epimethylcryptopines, designated as A and B (XXIX), which are believed to be the keto and enol forms of a compound arising from migration of the carbonyl oxygen of γ-methylcryptopine from C-14 to C-13. The isomers A and B are interconvertible. A third substance resulting from the reaction, isoepimethylcryptopine (XXX), is considered to be formed through interaction of the vinyl group with the double linkage arising from enolization in γ-methylcryptopine.



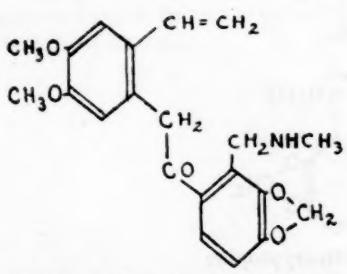
XXIX. Epimethylcryptopines A and B.



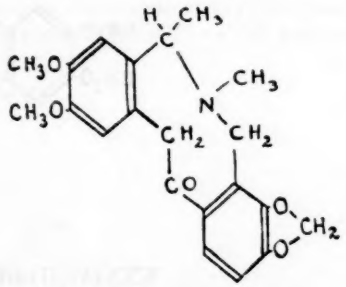
XXX. Isoepimethylcryptopine

The isomerism of the epimethylcryptopines and the mechanism assumed for the formation of isoepimethylcryptopine is held to be consistent with the location of the carbonyl group in the position shown in the cryptopine formula.

The epicryptopines (9) are analogous to the epimethylcryptopines in many ways. They are formed when anhydrocryptopine is heated with concentrated hydrochloric acid, and in contrast to cryptopine are thought to have the carbonyl group at C–13. As in the case of the methyl analogs, epicryptopine-A and-B (XXXI) are considered to be keto and enol forms of one substance. Epicryptopine-A, which forms a nitroso compound, is converted to a third isomer, epicryptopine-C (XXXII) on boiling with ethyl acetate. Epicryptopine-B yields an N-acetyl derivative, which can also be obtained with difficulty from isomer-C. Phosphorous oxychloride acts upon isomer-A to produce a colored salt, epicryptopirubin chloride (9).

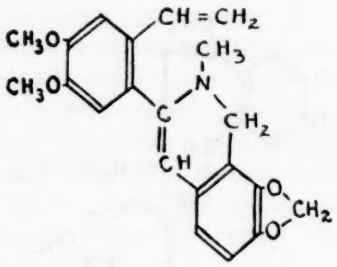


XXXI. Epicryptopines A and B.

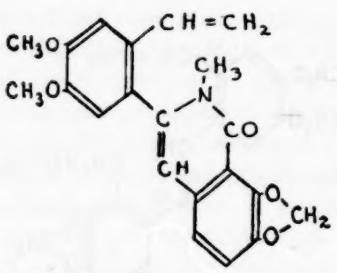


XXXII. Epicryptopine-C

ANHYDROCRYPTOPINE: As mentioned above, the action of alkali on isocryptopine chloride results in ring scission between C-6 and nitrogen, with the formation of the vinyl derivative, anhydrocryptopine (XI) (9). An active methylene group is present at C-8, which accounts for the coupling reaction shown with diazobenzene. By oxidation of this methylene group with potassium permanganate (9), ketoanhydrocryptopine (XXXIII) is obtained.



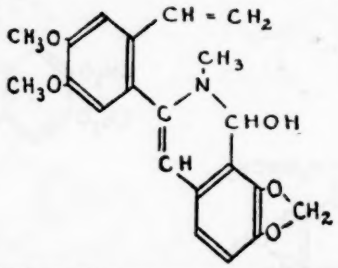
XI. Anhydrocryptopine



XXXIII. Ketoanhydrocryptopine

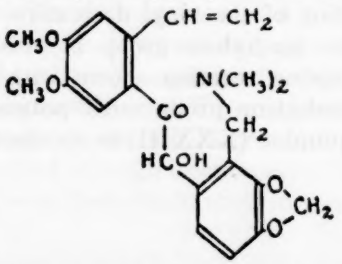
Ketoanhydrocryptopine can be further oxidized by permanganate to norketoanhydrocryptopic acid, which reduces with boiling formic acid to a dihydro derivative. Ketoanhydrocryptopine is converted by phosphorous oxychloride to the highly-colored ketoisoepicryptopirubin.

Through air oxidation (9) of anhydrocryptopine in boiling methyl alcohol, isomeric methoxyanhydrocryptopines (A and B) are obtained, in which a methoxyl group has replaced one hydrogen atom in the active methylene group. From the methoxy derivatives, acids split out methyl alcohol, yielding a yellow quaternary isoquinoline salt, which can be converted by the action of alkali into hydroxyanhydrocryptopine (XXXIV), an isoquinoline pseudo-base type. The pseudo-base is converted back to methoxyanhydrocryptopine by boiling with methyl alcohol or can be oxidized to the above-mentioned ketoanhydrocryptopine.



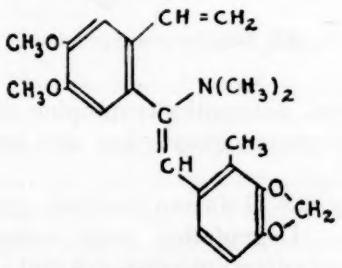
XXXIV. Hydroxyanhydrocryptopine

In contrast to the permanganate oxidation of the base itself, anhydrocryptopine methomethylsulphate with this reagent goes to dioxymethylisoanhydrodihydrocryptopine (XXXV) (22).

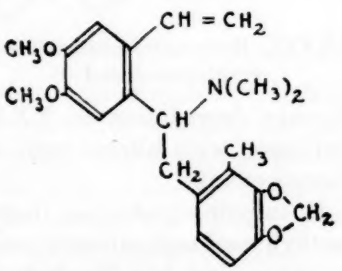


XXXV. Dioxymethylisoanhydrodihydrocryptopine

The metho derivatives of anhydrocryptopine, instead of undergoing ring scission with alkali, lose the added methyl group and regenerate the starting material (9). This unusual behavior has been observed also in the case of the analogous berberine derivatives (35), and in attempted degradations in the thebaizone series (36) (see p. 297). Reductive degradation (22) of anhydrocryptopine methomethylsulphate with sodium amalgam proceeds with scission of the 7, 8-linkage in the remaining isoquinoline ring giving dihydroanhydromethylcryptopine (XXXVI). When sodium amalgam in acid solution is used, reduction of the 13, 14-double bond takes place as well, to yield tetrahydroanhydromethylcryptopine (XXXVII).



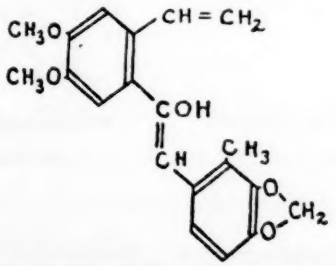
XXXVI. Dihydroanhydromethylcryptopine



XXXVII. Tetrahydroanhydromethylcryptopine

Tetrahydroanhydromethylcryptopine (22) is isomeric with anhydrotetrahydromethylcryptopine (XIX) already mentioned as resulting from dehydration of tetrahydromethylcryptopine and from the Hofmann degradation of tetrahydroanhydroisocryptopine, and is closely related to it. On further degradation it yields the same end product, cryptopidene (VII).

Dihydroanhydromethylcryptopine (22) may be oxidized to methylpiperonal, or may be further degraded to hydroxycryptopidene, XXXVIII (which may have the ketone formula).

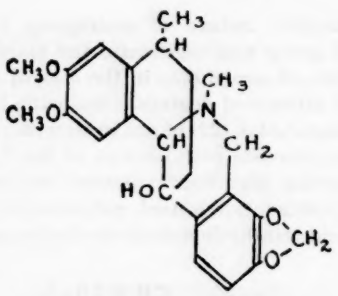


XXXVIII. Hydroxycryptopidene

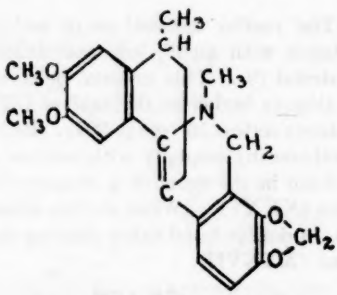
Hydroxycryptopidene oxidizes yielding methyl piperonylic acid and 4, 5-dimethoxy-2-vinyl-benzaldehyde (22).

The formation of the epicryptopines from the action of concentrated hydrochloric acid on anhydrocryptopine has already been mentioned.

When boiled with dilute hydrochloric acid anhydrocryptopine undergoes a change which has been interpreted as a hydration and an isomerization involving the vinyl group. Two isomers, hydroxyisoanhydrodihydrocryptopines-A and -B, XXXIX (probably stereoisomers), are produced. These can be dehydrated to the parent substance of the iso-series, isoanhydrocryptopine (9), XL.



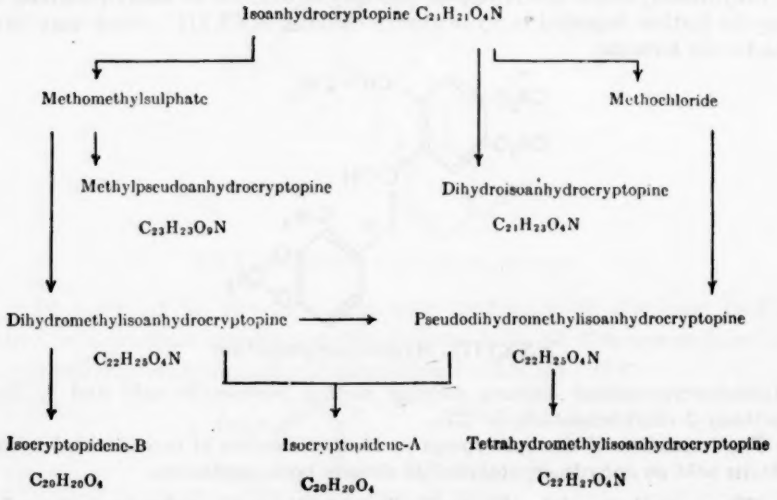
XXXIX. Hydroxyisoanhydrodihydrocryptopine-A and -B



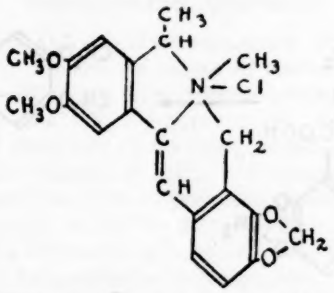
XL Isoanhydrocryptopine

Further degradation of XXXIX gives β-isomethylcryptopine (9). Oxidation with nitrous acid and with permanganate has also been carried out (9).

Isoanhydrocryptopine, degraded by the Hofmann method, gives methylpseudoanhydrocryptopine (9). Degradation with sodium amalgam gives two dihydromethylisoanhydrocryptopines (-A and -B) (22) which may be rearranged into a third isomer. The methomethylsulphates of these three isomers are all converted to the same isocryptopidene-A by alkaline reduction at 30°. Isocryptopidene-B results when dihydromethylisoanhydrocryptopine is reduced in boiling alkaline solution. Other less important products from these degradations are shown on the following diagram.

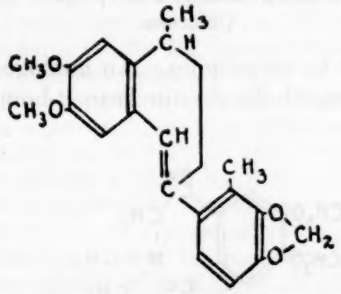


PSEUDOCRYPTOPINE SERIES: The metho derivatives of anhydrocryptopine, when heated with concentrated hydrochloric acid, yield the parent substance of the pseudo-series, pseudocryptopine chloride (9) (XLI) an isomer of isocryptopine chloride.

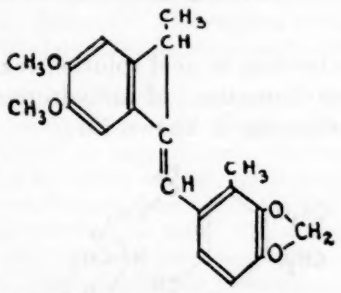


XLI. Pseudocryptopine chloride

The reactions of pseudocryptopine chloride differ considerably from those of isocryptopine chloride (22). Alkaline sodium amalgam reduction yields an isomer of anhydrodihydrocryptopine-A, namely pseudoanhydrodihydrocryptopine-A, which is considered to have a 9-membered ring. It can be degraded through the methomethylsulphate with sodium amalgam to pseudocryptopidene, XLII, an isomer of cryptopidene. When pseudocryptopine chloride is reduced in acid solution with sodium amalgam, loss of nitrogen, probably as methylamine takes place, and isopseudocryptopidene, XLIII, is formed, together with dihydroanhydropseudocryptopine.



XLII. Pseudocryptopidene

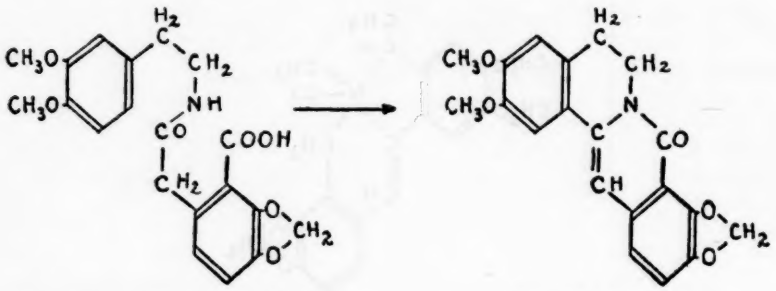


XLIII. Isopseudocryptopidene

The structure assigned to these isomers is supported to a certain extent by the results of oxidation (22).

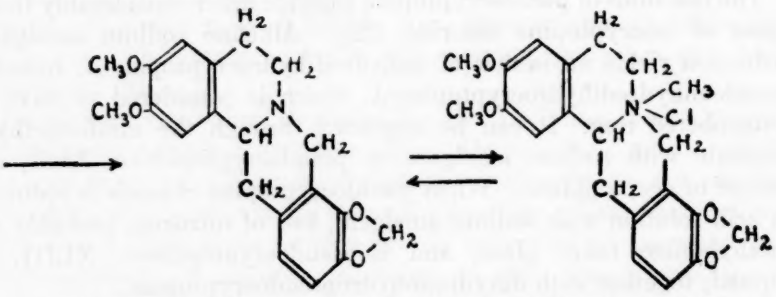
The synthesis of cryptopine was carried out by Haworth and Perkin (25) in 1926. It has its starting point in the condensation of homoveratrylamine with 3,4-methylenedioxyhomophthalic anhydride, with subsequent closure of two rings through the action of phosphorous oxychloride, to oxyepiberberine. The reduction product from this is tetrahydro (anhydro) epiberberine whose isomeric methochlorides are identical with α- and β- isodihydrocryptopine chlorides.

The isodihydrocryptopine chlorides have been converted to anhydrodihydrocryptopine-A as described above. (Plate I.) The latter substance oxidizes with perbenzoic acid to give an amine oxide, which



N-β-Veratrylethyl-3,4-methylenedioxyhomophthalamic Acid

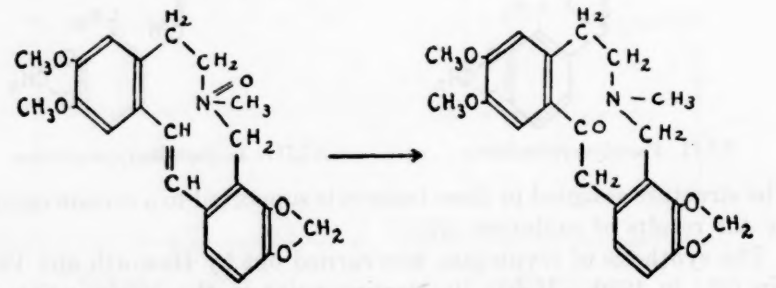
Oxyepiberberine



Tetrahydroanhydroepiberberine

α- and β- Isodihydrocryptopine Chlorides

on heating in acid solution rearranges to cryptopine. An analogous transformation, of anhydrotetrahydromethylberberine into β-homochelidonine is known (37).



Anhydrodihydrocryptopine-A Amine Oxide

Cryptopine

This synthesis of cryptopine does not offer very convincing evidence concerning the location of the cryptopine carbonyl group.

The cryptopine series has also been related to the berberines (25) (38) through anhydrocryptopine. Tetrahydro(anhydro)epiberberine oxidizes to epiberberinium chloride, from which dihydro(anhydro)epiberberine and oxyepiberberine can be obtained. Dihydro(anhydro)epiberberine degrades to anhydrocryptopine, or is formed by distillation of isocryptopine chloride under reduced pressure.

Descriptive Part (Cryptopine)

CRYPTOPINE, B=$C_{21}H_{23}O_5N$. —HYDROCHLORIDE (2) (5) (9) (30): B·HCl (+5H_2O or 6H_2O) (30). Gelatinous masses of feathery crystals prep. by the action of hydrochloric acid on the base; dries to brittle crust; sol. in water and chloroform, decomp. at 235° (9). —NITRATE (9), B·HNO_3, gelatinous mass formed by the action of nitric acid on the base, becoming crystalline; cryst. from dil. nitric acid as needles, decomp. at 115°. —HYDRIODIDE (9), B·HI, obtained as jelly. Boiling converts this to short prismatic crystals; slightly sol. in water. It darkens at 225°, decomp. at 235° to 240°. —OXALATE (8) (9), B·$C_2H_2O_4$+4H_2O, prep. by dissolving the base in an excess of oxalic acid. It cryst. as prisms from water and is used for purification of cryptopine. Crystal measurements, Perkin (9). —ACID TARTRATE (9), B·$C_4H_6O_6$+4H_2O, sl. sol. in cold water (1 :167 at 10°) and in alcohol; sol. in hot water or alcohol, and cryst. from these solvents. —NEUTRAL MECONATE (7) (39), B_2·$C_7H_4O_7$ (+10H_2O), silky needles, slightly sol. in water (1 : 1300 at 14.5°) (7). —PICRATE (7) (39) (40) yellow needles from 75% alcohol; m. p. 161° to 163° (corr.) (40) 215° (5). —ACID SULPHATE (39), crystalline. —β-BROMOCAMPHORSULPHONATE (9), B·$C_{10}H_{15}O_4BrS$, cryst. as nodular masses of woolly needles from water, ethyl acetate, or ethyl acetate-alcohol mixture. It softens at 180° and m. at 190° to 195°; $[\alpha]_D$=+37.8° to 40.8°, (water, p=1.5). —BICHROMATE (5) (39) fine yellow prisms. —MERCURICHLORIDE (5), colorless crystals, m. p. ca. 185°. —AURICHLORIDE (5), lemon-yellow needles, darkening at 200°, decomp. ca. 205°. —PLATINICHLORIDE (2) (5) (39), yellow needles, m. p. 204° (decomp.) (5).

CRYPTOPINE METHOMETHYLSULPHATE (9): B·$(CH_3)_2SO_4$+CH_3OH, cryst. as prismatic needles from methanol and from water; softens at 225°, m. at 235° to 238°. CRYPTOPINE METHIODIDE (9), B·CH_3I, cryst. as prisms from methanol or hot water, softens at 210°, m. at 215° to 217° (decomp.). CRYPTOPINE METHOCHLORIDE (9), B·CH_3Cl, prep. by the action of silver chloride on the methiodide; microscopic crystals.

NITROCRYPTOPINE (9) (30): $C_{21}H_{22}(NO_2)O_5N$, obtained as a by-product from the action of dil. or conc. nitric acid on cryptopine. It cryst. as prisms from alcohol, m. p. 187° to 189°. —Nitrate, cryst. in small prisms. DINITROCRYPTOPINE-A (9), $C_{21}H_{21}(NO_2)_2O_5N$, prep. by the action of conc. nitric acid at 25° on cryptopine. Isolated as the pale yellow Nitrate, from which the base is precipitated with ammonia. It is crystalline, but does not melt. The salts are difficultly soluble; Hydrochloride, prisms, and Sulphate have been prepared. DINITROCRYPTOPINE-B (9), $C_{21}H_{21}(NO_2)_2O_5N$, isolated from the mother liquors of preparation of isomer-A. Obtained as a cryst. crust from conc. acetone solution; microscopic prisms from alcohol, m. p. 213° (decomp.). The base and salts are more soluble than the A series. Crystalline salts obtained are Nitrate, Mercurichloride, Platinichloride, and Picrate.

CRYPTOPIDIC ACID (9): $C_{18}H_{21}O_7N$, prep. by heating cryptopine with conc. nitric acid, or in small amounts as a by-product from the action of dil. nitric acid. It cryst. as amber prisms from water and darkens at 175°, m. at 185° to 187° (decomp.). Acetic-sulphuric acid mixture gives a carmine color. —SILVER SALT, $C_{18}H_{19}O_7NAg_2$, chalky precipitate. —HYDROCHLORIDE, $C_{18}H_{21}O_7N$·HCl, lemon-yellow cryst. mass from conc. hydrochloric acid. It darkens at 180° and decomp. at 202° and is hydrolyzed by boiling water. —ACETATE, $C_{20}H_{25}O_9N$, obtained from acetic acid solution; darkens at 175°, decomp. at 197° to 200°.

ISOCRYPTOPINE. —CHLORIDE (9), $C_{21}H_{22}O_4NCl$, prep. by heating cryptopine with phosphorous oxychloride. Cryst. from water or 2% hydrochloric acid. It turns yellow at 130°, darkens at 210° to 220° and melts ca. 223° (decomp.); it is not precipitated by ammonia. —PLATINICHLORIDE, $(C_{21}H_{22}O_4NCl)_2PtCl_4$, yellow cryst. precipitate. —AURICHLORIDE, $C_{21}H_{22}O_4NClAuCl_3$, drab-purple

precip. —IODIDE, $C_{21}H_{22}O_4NI$, granular cryst. from water, darkening at 170° to 190°, and melting at 245° to 247° (decomp.). —DISULPHATE, $C_{21}H_{22}O_4NHSO_4 \cdot H_2SO_4$, prep. by heating cryptopine with acetic and sulphuric acids and cryst. from water. It darkens at 230° to 245°, and decomp. at 250°. Conc. H_2SO_4 gives a blue-violet, nitric acid a blue color. The salt is light-sensitive, turning blue. —DICHLORIDE, $C_{21}H_{22}O_4NCl \cdot HCl$, prep. by the action of conc. hydrochloric acid on the disulphate. FREE BASE: ISOCRYPTOPINE HYDROXIDE (?), obtained as a jellylike mass when isocryptopine disulphate is treated with barium hydroxide. —SULPHATE, $(C_{21}H_{22}O_4N)_2SO_4 + 7CH_3OH$, prepared by the action of ammonia on the disulphate. Cryst. from dil. ammonia; darkens at 140° to 200°, melts to a tar at 215° to 220°. It cryst. from methanol as a gelatinous mass turning into prismatic crystals.

ETHYLDIHYDROISOANHYDROCRYPTOPINE (9). —BROMIDE, $C_{23}H_{30}O_4NBr$, prep. by the action of ethyl magnesium bromide on isocryptopine chloride. It cryst. as prisms from alcohol, darkens at 220°, m. p. 227° (decomp.). —IODIDE, $C_{23}H_{26}O_4NI$, red-ochreous cryst. mass, decomp. at 228° to 230°.

α-ISODIHYDROCRYPTOPINE. —CHLORIDE (9): $C_{21}H_{24}O_4NCl(+4H_2O)$, prep. (along with the β-isomer) by the action of acetyl chloride or phosphorous oxychloride on dihydrocryptopine; formed also during the reduction of cryptopine (see also similar reaction with benzoyl chloride (21)); prepared (25) (along with the β-isomer) by electrolytic reduction of isocryptopine chloride and by methylating tetrahydroepiberberine. It may be isolated from the mother liquors after separation of the less soluble β-isomer and cryst. as prisms from conc. aqueous solution; softens at 145°, m. at 165°, resolidifies, darkens at 200° and decomp. at 230°. The Hydrate (air dried) m. at 80° to 85° and resolidifies. The Grignard reagent is without action. —BROMIDE, $C_{21}H_{24}O_4NBr$, cryst. from water as clusters of needles; darkens at 235°, unmelted at 270°. —IODIDE, cryst. from water as 4-sided truncated prisms, darkening at 225° to 230°, and m. at 275° to 280° (decomp.). —MERCURICHLORIDE, crusts of prisms from water; crystal measurements given. —PLATINICHLORIDE, yellow cryst. precip; darkens at 200°, decomp. at 210° to 215°.

β-ISODIHYDROCRYPTOPINE. —CHLORIDE (9) (25) $C_{21}H_{24}O_4NCl$, obtained in the reaction described for the α-isomer, and also as a by-product of sodium amalgam reduction of isocryptopine chloride (22). It cryst. as voluminous needles from water, in which it is slightly sol; darkens at 210°, unmelted at 260°. —PLATINICHLORIDE (9), ochreous chalky precipitate, darkens at 240°, decomp. at 250° to 253°. —IODIDE, $C_{21}H_{24}O_4NI$, granular leafy cryst. masses.

DIHYDROCRYPTOPINE (9) (Hydrocryptopine (21)): $B = C_{21}H_{25}O_5N$, obtained by sodium amalgam reduction of cryptopine in dil. sulphuric acid; isolated as cryst. crusts from conc. ether solution, and separated from cryptopine as the more soluble OXALATE (9) (needles from conc. soln.). The base cryst. as prisms from alcohol, m. p. 187° to 188°. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$, and —MERCURICHLORIDE, are crystalline. —PICRATE, amorphous (9).

DIHYDROMETHYLCRYPTOPINE (22): $C_{22}H_{27}O_5N$, prep. by reducing cryptopine methochloride with sodium amalgam in alkaline solution; cryst. as prismatic needles from a methanol-ether mixture; m. p. 118° to 120°. —HYDROCHLORIDE, microscopic prisms.

TETRAHYDROMETHYLCRYPTOPINE (9): $B = C_{22}H_{29}O_5N$, prep. by sodium amalgam reduction of cryptopine methomethylsulphate in acid solution. Cryst. as prisms from conc. ether solution, and from benzene or petroleum ether; m. p. 106° to 107°. —HYDROCHLORIDE, prismatic needles. —NITRATE, crystalline. —HYDRIODIDE, cryst. from water. —MERCURICHLORIDE, crystalline. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$, pale yellow precip. —AURICHLORIDE and —PICRATE amorphous.

ANHYDROTETRAHYDROMETHYLCRYPTOPINE (9): B=$C_{22}H_{27}O_4N$ (+CH_3OH), prep. by boiling tetrahydromethylcryptopine with phosphorous oxychloride or acetyl chloride, or by exhaustive methylation of tetrahydroanhydroisocryptopine (22). Cryst. from methanol as prisms, m. p. 106° to 108° (22). Crystal measurements have been made. The base gives fluorescent solutions, and the salts fluoresce in the dry state but not in solution. —HYDROCHLORIDE, B·HCl, felted mass of needles. —NITRATE, insol. in dil. nitric acid. —MERCURICHLORIDE, crystalline. —PICRATE, crystalline. —PLATINICHLORIDE, $B_2·H_2PtCl_6$, chalky precipitate. —METHOMETHYLSULPHATE, $C_{22}H_{27}O_4N(CH_3)_2SO_4$, cryst. from water, sinters at 130°, m. about 195° to 197°.

CRYPTOPIDENE (9): (4,5-dimethoxy-3′,4′-methylenedioxy-6-methyl-2-vinylstilbene), $C_{20}H_{20}O_4$, prep. by the action of methyl alcoholic potassium hydroxide on the methomethylsulphate of anhydrotetrahydromethylcryptopine (9), or of tetrahydroanhydromethylcryptopine (22); it cryst. from alcohol as warty masses or striated needles, m. p. 124°. Solutions of cryptopidene are fluorescent. The base adds four atoms of bromine. TETRAHYDROCRYPTOPIDENE (22): $C_{20}H_{24}O_4$, prep. by reduction of cryptopidene with sodium and alcohol; cryst. as prisms (fluorescent) from methanol, m. p. 78°.

ANHYDROCRYPTOPINE (9): B=$C_{21}H_{21}O_4N$, obtained by the action of methyl alcoholic potassium hydroxide on isocryptopine chloride or sulphate, and from anhydrocryptopine methiodide or methomethylsulphate, by heating with alkali; cryst. as lemon-yellow or colorless prisms from methanol, m. p. 110° to 111°. Crystal measurements given. The base gives a red-brown precip. with benzenediazonium chloride, and a brick-red powder with nitrous acid. —HYDRIODIDE, B·HI, crystalline, darkens above 170°, m. p. 195°. —PLATINICHLORIDE, $B_2·H_2PtCl_6$. —MERCURICHLORIDE, crystalline. —METHOMETHYLSULPHATE (see also Perkin (22): (B·$(CH_3)_2SO_4$, cryst. as flat needles from methanol or water; darkens at 225° to 227°, m. p. 238° to 240° (decomp.). Crystal measurements given. —METHIODIDE (9), B·CH_3I, cryst. as microscopic prisms from methanol; darkens above 170°, m. at 188° to 192° (decomp.). —METHOCHLORIDE, B·CH_3Cl, cryst. as lemon-yellow prisms from methanol, m. p. 223° to 225° (decomp.). —METHOCHLORIDE PLATINICHLORIDE, $(B·CH_3Cl)_2PtCl_6$, darkens above 200°, m. 210° to 212° (decomp.). —ETHIODIDE, B·C_2H_5I, cryst. as orange-red needles from alcohol, m. p. 228° to 230° (decomp.). —METHYL HYDROGEN SULPHATE (22) B·CH_3HSO_4, a by-product of the preparation of the methomethylsulphate.

METHYLANHYDROCRYPTOPINE (9): —METHIODIDE, $C_{22}H_{23}O_4NCH_3I$, obtained as a by-product from the action of methyl iodide on anhydrocryptopine. Cryst. as sulphur-yellow prisms from methanol; darkens at 185°, decomp. gradually. The free base was obtained by the action of alkali on the methiodide as a gum which crystallized. —METHOPLATINICHLORIDE, $(C_{23}H_{25}O_4N)_2PtCl_6$.

ETHYLANHYDROCRYPTOPINE ETHIODIDE (9): $C_{23}H_{25}O_4N·C_2H_5I$, obtained as a by-product of the action of ethyl iodide on anhydrocryptopine as crimson needles, m. p. 290° to 295° (decomp.).

DIOXYMETHYLISOANHYDRODIHYDROCRYPTOPINE (22): $C_{22}H_{25}O_6N$, prep. by permanganate oxidation of anhydrocryptopine methochloride; cryst. as needles from alcohol or acetone, m. p. 187° to 188°. It reduces chlorauric acid and gives color reactions with acids. The SEMICARBAZONE and PLATINICHLORIDE were prepared.

DIHYDROANHYDROMETHYLCRYPTOPINE (22): B=$C_{22}H_{25}O_4N$, prep. by sodium amalgam reduction of anhydrocryptopine methomethylsulphate in alkaline medium; amorphous. —PLATINICHLORIDE, $B_2·H_2PtCl_6$, chalky. —METHOMETHYLSULPHATE, B$(CH_3)_2SO_4$, cryst. as prisms from water, m. p. 210°. —METHIODIDE, B·CH_3I, cryst. in spangles, m. p. ca. 217° (decomp.).

HYDROXYCRYPTOPIDENE (22): $C_{20}H_{20}O_5$, obtained by the action of alkali on the methomethylsulphate of dihydroanhydromethylcryptopine; cryst. from ether

or methanol as nodules of chisel-shaped prisms of m. p. 88° to 89°. β-HYDROXYISOCRYPTOPIDENE (22): (a polymeride (?)), $C_{20}H_{20}O_5$, obtained from hydroxycryptopidene by heating with acetyl chloride; shrivels at 175° to 180°, froths at 200°.

TETRAHYDROANHYDROMETHYLCRYPTOPINE (22): B=$C_{22}H_{27}O_4N$, obtained by acidic reduction of anhydrocryptopine methomethylsulphate with sodium amalgam; amorphous. —HYDROCHLORIDE, noncrystalline. —PLATINICHLORIDE, chalky. —METHOMETHYLSULPHATE, noncrystalline.

ANHYDRODIHYDROCRYPTOPINE-A (9): B=$C_{21}H_{23}O_4N$, obtained along with the B-isomer by the action of methyl alcoholic KOH or silver hydroxide on α- or β-isodihydrocryptopine chlorides. It is slightly sol. in cold alcohols, acetone and benzene, and cryst. from alcohol as balls of needles, from acetone or benzene as 4-sided prisms of m. p. 178°. The salts are more soluble than those of the B-isomer. —HYDROCHLORIDE, microscopic balls of needles from conc. aqueous solution; darkens at 200° to 230°, not melted at 250°. —SULPHATE, warty masses from conc. solution. —HYDRIODIDE, cryst. as warty masses. —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6$, crystalline, slightly sol. in water, darkens at 200° and decomp. at 215° to 220°. —METHOMETHYLSULPHATE, $B(CH_3)_2SO_4$, cryst. from alcohol as flat microscopic needles; shrinks at 190°, m. p. 240° to 242°. —METHIODIDE, $B{\cdot}CH_3I$, cryst. as prisms from alcohol; colors and shrinks at 230°, m. p. 235° to 240° (gums). —METHOCHLORIDE, $B{\cdot}CH_3Cl$, obtained by the action of silver chloride on the methiodide, pasty crusts, decomp. 215° to 220°.

ANHYDRODIHYDROCRYPTOPINE-B (9): B=$C_{21}H_{23}O_4N$, obtained along with the A-isomer by the action of alkali on isodihydrocryptopine chloride, or from the A-isomer by boiling with alcohol, or by reduction of anhydrocryptopine. Cryst. as brilliant prisms from methanol, m. p. 126° to 127°. Cryst. measurements given. —HYDROCHLORIDE, $B{\cdot}HCl$, cryst. as slender needles, m. p. 225° (decomp.) —SULPHATE, 4-sided plates. —HYDRIODIDE, crystalline. —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6$, cryst. of m. p. 223° (decomp.). —METHOMETHYLSULPHATE, $B(CH_3)_2SO_4$, cryst. as 4-sided plates from methanol or water, m. p. 245° (decomp.). —METHIODIDE, $B{\cdot}CH_3I$, cryst. in granules from water and as microscopic 4-sided plates from methanol, m. p. 238°. —METHOCHLORIDE, $B{\cdot}CH_3Cl$, obtained as pale yellow crystalline crusts by the action of silver chloride on the methiodide, m. p. 240° (decomp.).

METHYLISOANHYDRODIHYDROCRYPTOPINE (9): B=$C_{22}H_{25}O_4N$, obtained by the action of alkali on anhydrodihydrocryptopine-A and -B. Cryst. from methanol as needles of lilac fluorescence, m. p. 106°. The salts show little tendency to crystallize. —HYDRIODIDE is crystalline. —PLATINICHLORIDE darkens at 190°, decomp. at 195° to 200°. —METHOMETHYLSULPHATE, $B(CH_3)_2SO_4$, cryst. as flat needles from water or alcohol (fluorescent), softens at 210°, m. at 215°. —METHIODIDE, cryst. from water or alcohol as prismatic needles, m. p. 215° to 217° (decomp.). —METHOCHLORIDE, shellaclike mass containing cryst. nodules.

α-ISOCRYPTOPIDOL (9): $C_{20}H_{20}O_5$, obtained with the β-isomer by the action of alkali on methylisoanhydrocryptopine methomethylsulphate. Cryst. from methanol, m. p. 90° to 92°. β-ISOCRYPTOPIDOL (9), $C_{20}H_{20}O_5$, obtained in the prep. of the α-isomer; amorphous, softens at 235°, not melted at 260°.

HYDROXYTETRAHYDROANHYDROCRYPTOPINE (9): $C_{21}H_{25}O_5N$, obtained by the action of dil. acid on anhydrodihydrocryptopine-B; amorphous, chalky consistency, m. p. ca. 70°. The salts are soluble. —PLATINICHLORIDE, chalky. —SULPHATE, 4-sided prisms, m. p. 150° (decomp.). —HYDRIODIDE, prisms, m. p. 155° to 158° (decomp.).

DIHYDROANHYDROISOCRYPTOPINE (22): B=$C_{21}H_{23}O_4N$, one of the sodium amalgam reduction products of isocryptopine chloride. Cryst. as needles from alcohol or acetone, m. p. 195°. —HYDROCHLORIDE, $B{\cdot}HCl$, cryst. as needles from

dil. hydrochloric acid. —NITRATE, crystalline. —HYDRIODIDE, B·HI, cryst. as warty aggregates from alcohol, m. p. 250° to 255° (decomp.).

TETRAHYDROANHYDROISOCRYPTOPINE (22): B=$C_{21}H_{25}O_4N$, obtained by the reduction of isocryptopine chloride in acid solution with sodium amalgam. Cryst. as striated prismatic needles from methanol; cryst. also from acetone and benzene, m. p. 138° to 139°. The salts are soluble and cryst. from conc. acid solutions as needles. —PLATINICHLORIDE, cryst. as irregular plates from water. —MERCURICHLORIDE, crystalline. —METHOMETHYLSULPHATE, B$(CH_3)_2SO_4$, softens at 145°, m. at 160°. —METHIODIDE, B·CH_3I, cryst. as glistening needles from water, m. p. 263°.

DIHYDROANHYDRODIHYDROCRYPTOPINE-A (22): B=$C_{21}H_{25}O_4N$, obtained as a by-product of the sodium amalgam reduction of isocryptopine chloride in acid solution. Obtained also by reduction of anhydrodihydrocryptopine-A with sodium amalgam. Cryst. as stars of flat needles from methanol, m. p. 163° to 164°. —HYDROCHLORIDE, flat needles. —SULPHATE, radiating hairs. —NITRATE, prismatic needles. —PLATINICHLORIDE, microscopic balls of needles. —MERCURICHLORIDE, stars of prisms from water. —PICRATE, yellow. —METHOMETHYLSULPHATE, B$(CH_3)_2SO_4$, soft needles.

DIHYDROISOANHYDRODIHYDROMETHYLCRYPTOPINE (22): B=$C_{22}H_{27}O_4N$, obtained by the action of methyl alcoholic KOH on the methomethylsulphate of dihydroanhydrodihydrocryptopine-A. Cryst. as brilliant prisms (measurements given) from conc. ether solution, m. p. 75° to 77°. The salts are soluble. —PLATINICHLORIDE, chalky salmon precip.

DIHYDRO-α-ISOCRYPTOPIDOL (22): $C_{20}H_{22}O_5$, obtained by exhaustive methylation of dihydroisoanhydrodihydromethylcryptopine; amorphous.

DIHYDROANHYDROTETRAHYDROMETHYLCRYPTOPINE (22): B=$C_{22}H_{29}O_4N$, obtained by sodium amalgam reduction of methomethylsulphates of tetrahydroanhydroisocryptopine or dihydroanhydrodihydrocryptopine-A. Cryst. from pet. ether, m. p. 60° to 63°. —HYDROCHLORIDE, cryst. from dil. hydrochloric acid or methanol as needles, m. p. 213°. —HYDRIODIDE, cryst. from methanol, m. p. 212°. —NITRATE, felted hairs. —METHOMETHYLSULPHATE, B$(CH_3)_2SO_4$, needles, m. p. 165° to 167°. —METHOBROMIDE, prismatic flat-ended needles. —METHIODIDE, B·HI, tufts of needles, darkens at 230°, m. at 240°.

DIHYDROCRYPTOPIDENE (22): $C_{20}H_{22}O_4$, obtained by the exhaustive methylation of dihydroanhydrotetrahydromethylcryptopine. Cryst. as a voluminous mass of needles from ether or methanol, m. p. 126° to 128°. KETODIHYDROCRYPTOPIDENE (22), $C_{20}H_{20}O_5$, obtained by permanganate oxidation of cryptopidene; cryst. from methanol, m. p. 116°. —Semicarbazone, $C_{21}H_{23}O_5N_3$, cryst. as needles from methanol, m. p. 185° to 190°. DIHYDROCRYPTOPIDENIC ACID (22), $C_{19}H_{20}O_6$, second product of oxidation of dihydrocryptopidene; cryst. as needles from water or alcohol, m. p. 194° to 195°. —Anilide, $C_{18}H_{19}O_4CONHC_6H_5$, cryst. from acetic acid as glistening needles, m. p. 185°.

α-METHYLCRYPTOPINE (9): $C_{22}H_{25}O_5N$, obtained as the main product (together with the β- and γ-isomers) by the action of methyl alcoholic KOH on cryptopine methomethylsulphate, also from the polymorphous β-isomer by dissolving in acid, precipitating with ammonia, and extracting with ether. Isolated as cryst. crusts from ether, ethyl acetate or acetone, m. p. 151° to 153°.

β-METHYLCRYPTOPINE (9): B=$C_{22}H_{25}O_5N+CH_3OH$, obtained with the α- and γ-isomers by the action of alkali on cryptopine methomethylsulphate, or from the α-form by heating with methanol. Cryst. from alcohol, m. p. 127° to 128°. It does not give an oxime. —HYDROCHLORIDE, gelatinous, m. p. 180° to 182° (decomp.). —NITRATE and —SULPHATE, not crystalline. —HYDRIODIDE. B·HI, crystalline, m. p. 230° to 235°. —PLATINICHLORIDE, $B_2·H_2PtCl_6$, cryst., darkens at 190°, decomp. at 210° to 215°. —METHOMETHYLSULPHATE, B$(CH_3)_2SO_4$,

cryst. from methanol as voluminous mass of microscopic needles, m. p. 275° (decomp.). —METHIODIDE, chalky.

γ-METHYLCRYPTOPINE (9): B=$C_{22}H_{25}O_5N$, prep. from cryptopine methochloride or methomethylsulphate by the action of alkali; forms prisms from alcohol, acetone or ether, m. p. 110°; not reduced by sodium amalgam. —SULPHATE, microscopic needles. —HYDRIODIDE, B·HI, cryst. from water or alcohol as flat needles, m. p. 188°. —PLATINICHLORIDE, cryst. precip. —METHOMETHYLSULPHATE, cryst. from methanol; is unstable. —OXIME, $C_{22}H_{26}O_5N_2$, amorphous. —SEMICARBAZONE, $C_{23}H_{28}O_5N_4$, cryst. crusts m. p. 185°. —SEMICARBAZONE HYDROCHLORIDE ACETATE, $C_{23}H_{28}O_5N_4 \cdot C_2H_4O_2 \cdot HCl$, crystalline, softens at 200°, m. at 228° to 230°. —OXIDATION PRODUCT, $C_{22}H_{21}O_9N$, chalky. ACETYL-γ-METHYLCRYPTOPINE (9), B=$C_{24}H_{27}O_6N$, cryst. in prisms from methanol, m. p. 94° to 95°; hydrolyzes with methyl alcoholic KOH; –Hydrochloride, B·HCl, silvery mass from dil. hydrochloric acid, m. p. 205° to 206°; –Hydriodide, B·HI, cryst. as glistening scales from water or methanol, m. p. 184° (decomp.). –Platinichloride, $B_2 \cdot H_2PtCl_6$, yellow chalky precip.

CRYPTOPIDIOL (9): $C_{20}H_{20}O_6$, obtained as a by-product in the exhaustive methylation of the methylcryptopines; ochreous flakes, darkens at 250°.

ANHYDROCRYPTOPIDIOL (9): $C_{20}H_{18}O_5$, obtained by the exhaustive methylation of β- and γ-methylcryptopines. Precip. as flocks from benzene with petroleum ether, m. p. 107° to 109°.

EPIMETHYLCRYPTOPINE-A (9): $C_{22}H_{25}O_5N$, obtained by the action of conc. hydrochloric acid on γ-methylcryptopine; cryst. as chalky powder from benzene, m. p. 222° to 223°. The salts are sparingly soluble. EPIMETHYLCRYPTOPINE-B (9), $C_{22}H_{25}O_5N$, obtained as a by-product along with the A-isomer; an ochreous powder. ISOEPIMETHYLCRYPTOPINE (9), $C_{22}H_{25}O_5N$, obtained from the filtrates from the treatment of γ-methylcryptopine with HCl; amorphous; –Hydrochloride apparently crystalline; –Platinichloride, plum colored precip.

PSEUDOCRYPTOPINE (9) (22): —CHLORIDE, $C_{21}H_{22}O_4NCl+6H_2O$, prep. by the action of hydrochloric acid on anhydrocryptopine methomethylsulphate or methochloride. Cryst. as needles from dil. hydrochloric acid m. p. 117° to 120°, foams at 150° to 152°. Anhydrous cryst. from methanol, darkens at 190°, m. at 210° (decomp.). —IODIDE (9) (22), dimorphous; cryst. from water as scales or needles (A), m. p. 232° to 235°; boiled with methanol, cryst. as prisms (B), m. p. 240° to 242°. —BROMIDE (22), ($+5H_2O$), dimorphous, cryst. from water as microscopic needles, m. p. 130° to 135°, solidifies and remelts at 230° (decomp.). Anhydrous product cryst. from alcohol as prisms, m. p. 245° (decomp.). —PLATINICHLORIDE (9), ochreous precip. —BLACK BASE, $C_{21}H_{18}O_4N$, obtained by boiling with alkali. —HYDROGEN SULPHATE (22), $C_{21}H_{22}O_4NHSO_4$, cryst. from dil. sulphuric acid, m. p. 215° to 220° (decomp.). —NITRATE (22), boat-shaped plates.

PSEUDOANHYDRODIHYDROCRYPTOPINE-A (22): B=$C_{21}H_{23}O_4N$, obtained by sodium amalgam reduction of pseudocryptopine chloride in alkaline medium. Cryst. as prisms from methanol (measurements given), m. p. 112°. —METHOMETHYLSULPHATE, $B \cdot (CH_3)_2SO_4$, cryst. as prismatic needles from water, m. p. 175° to 180° (decomp.). —METHIODIDE, $B \cdot CH_3I$, 6-sided prisms from water, or radiating prismatic needles from methanol, m. p. 197° to 200° (decomp.).

PSEUDOCRYPTOPIDENE (22): $C_{20}H_{20}O_4$, obtained by sodium amalgam (alkaline) reduction of pseudoanhydrodihydrocryptopine-A; cryst. as needles from methanol, m. p. 142° to 144°. DIOXYPSEUDOCRYPTOPIDENE (22), $C_{20}H_{18}O_6$, oxidation product of pseudocryptopidene. Cryst. as wooly balls from methanol, m. p. 138° to 140°; –Semicarbazone, $C_{21}H_{21}O_6N_3$, cryst., sl. sol. in methanol. TRIOXYPSEUDOCRYPTOPIDENE (22), $C_{20}H_{18}O_7$, oxidation product of pseudocryptopidene; cryst. as sulphur-yellow prismatic needles from methanol, m. p. 165°. —Disemicarbazone, $C_{22}H_{24}O_7N_6$, gelatinous precip.

DIHYDROANHYDROPSEUDOCRYPTOPINE (22): B=$C_{21}H_{25}O_4N$, obtained by reduction of pseudocryptopine chloride by sodium amalgam in acid medium; amorphous. —PICRATE, B·$C_6H_3O_7N_3$, cryst. as orange leaflets from methanol, m. p. 195° to 197°.

ISOPSEUDOCRYPTOPIDENE (22): $C_{20}H_{20}O_4$, obtained also as a product from sodium amalgam reduction (acid solution) of pseudocryptopine chloride; cryst. from methanol, acetone or acetic acid as plates, m. p. 150° to 152°. KETODIHYDROISOPSEUDOCRYPTOPIDENE (22), $C_{20}H_{20}O_5$, obtained by permanganate oxidation of isopseudocryptopidene; cryst. from methanol as glistening plates, m. p. ca. 135°; —Semicarbazone, $C_{21}H_{23}O_5N_3$, cryst. as needles from methanol; boiling conc. hydrochloric acid converts it into a new substance which cryst. as needles from methanol, m. p. 225°.

KETOANHYDROCRYPTOPINE (9): B=$C_{21}H_{19}O_5N$, obtained by the oxidation of anhydrocryptopine or hydroxyanhydrocryptopine with permanganate. Obtained also in attempted ethylation of anhydrocryptopine with diethyl sulphate; cryst. as needles from benzene, m. p. 163°.

BASE: $C_{21}H_{21}O_6N$, a by-product of oxidation of anhydrocryptopine; cryst. from ether, decomp. ca. 150°. Hydrochloric acid gives a QUATERNARY SALT. PLATINICHLORIDE, $(C_{21}H_{20}O_5N)_2PtCl_6$, chalky.

NORKETOANHYDROCRYPTOPIC ACID (9): B=$C_{20}H_{17}O_7N$, obtained by permanganate oxidation of ketoanhydrocryptopine or anhydrocryptopine. Difficult to crystallize; obtained as needles from methanol, m. p. 165°. DEHYDRONORKETOANHYDROCRYPTOPIC ACID (9), $C_{20}H_{15}O_6N$, obtained by boiling norketoanhydrocryptopine-A with formic acid. Cryst. from acetic acid as satiny needles having no definite melting point.

METHOXYANHYDROCRYPTOPINE-A (9): B=$C_{22}H_{23}O_5N$, obtained by boiling anhydrocryptopine or hydroxyanhydrocryptopine in methanol. Cryst. as almost colorless prisms from methanol, darkens above 160°, m. 186° to 188° (decomp.). It condenses with nitromethane and trinitrotoluene. METHOXYANHYDROCRYPTOPINE-B (9), $C_{22}H_{23}O_5N$, obtained from the mother liquors from the preparation of the A-isomer by exposure to air, as amber prisms from methanol, m. p. 160° to 162°.

ETHOXYANHYDROCRYPTOPINE-A (9): $C_{23}H_{25}O_5N$, obtained by boiling anhydrocryptopine with ethyl alcohol. Cryst. as pale brown crusts from alcohol, m. p. 152°. B-ISOMERIDE (?), cryst. from the mother liquors from the preparation of ethoxyanhydrocryptopine-A; m. p. 125° to 130°.

HYDROXYANHYDROCRYPTOPINE (9): $C_{21}H_{21}O_5N$. obtained by the action of hydrochloric acid, followed by alkali, on the methoxy or ethoxyanhydrocryptopines. Separates from ether as crusts of no definite melting point. —CHLORIDE, $C_{21}H_{20}O_4NCl$, cryst. as orange needles from acetone or water. —CYANIDE, chalky. —IODIDE, $C_{21}H_{20}O_4NI$, orange prisms from methanol, m. p. ca. 230° (decomp.). —PLATINICHLORIDE, $(C_{21}H_{20}O_4N)_2PtCl_6$, yellow precip. darkens ca. 240°.

HYDROXYISOANHYDRODIHYDROCRYPTOPINE-A (9): B=$C_{21}H_{23}O_5N$, obtained as the hydrochloride by boiling anhydrocryptopine with dil. hydrochloric acid or from the B-isomer by boiling the hydrochloride with methanol; amorphous, m. p. ca. 80° to 85°. —HYDROCHLORIDE, B·HCl, cryst. from water as needles of m. p. 227° (decomp.). —HYDRIODIDE, B·HI, cryst. from methanol as small prisms of m. p. 205° (decomp.). —PLATINICHLORIDE, $B_2·H_2PtCl_6$, darkens at 200°, decomp. at 210°. —METHOMETHYLSULPHATE, $B(CH_3)_2SO_4$, cryst. as rectangular plates from water, m. p. 190° to 192° (decomp.). —METHIODIDE, B·CH_3I, cryst. from water or alcohol in striated or twinned prismatic crystals; darkens at 180° melts at 200° to 202°. —ACID SULPHATE, B·H_2SO_4, cryst. from water as

ochreous nodules, m. p. 174° (decomp.). —BENZOYL DERIVATIVE, -Hydrochloride, $C_{28}H_{27}O_6N \cdot HCl$, satiny crystals from methanol, m. p. 235° (decomp.).

DIHYDROXYISOANHYDRODIHYDROCRYPTOPINE (9): $B = C_{21}H_{23}O_6N$, obtained by oxidation of hydroxyisoanhydrodihydrocryptopine-A with nitrous acid; cryst. crusts from ether. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$.

DIKETOTETRAHYDROANHYDROCRYPTOPINE (9): $C_{21}H_{21}O_6N$, obtained by permanganate oxidation of hydroxyisoanhydrodihydrocryptopine-A; cryst. as nodular masses from ether, m. p. 185° to 190°.

β–ISOMETHYLCRYPTOPINE (9): $B = C_{22}H_{25}O_5N$, obtained by exhaustive methylation of hydroxyisoanhydrodihydrocryptopine-A; amorphous. —HYDRIODIDE, B·HI, crystalline. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$, darkens at 205°, decomp. at 250° to 255°. —METHOMETHYLSULPHATE, amorphous, gives a blue-black substance, $C_{23}H_{23}O_5N$, when heated with methyl alcoholic KOH.

HYDROXYISOANHYDRODIHYDROCRYPTOPINE-B (9): $B = C_{21}H_{23}O_5N$, isolated from the mother liquors in the preparation of the A-isomer, or from the A-isomer by heating with acetyl chloride; amorphous. —HYDRIODIDE, B·HI, cryst. as needles, m. p. 175° to 177° (decomp.). —ACID SULPHATE, $B \cdot H_2SO_4$, cryst. as colorless prisms from water, m. p. 178° to 180° (decomp.).

ISOANHYDROCRYPTOPINE (9): $B = C_{21}H_{21}O_4N$, obtained by heating hydroxyisoanhydrodihydrocryptopines -A or -B, or anhydrocryptopine with conc. hydrochloric acid, or the former with phosphorous oxychloride. Cryst. as prisms (measurements given) from methanol, m. p. 158° to 160°. —HYDROCHLORIDE, B·HCl, cryst. from dil. hydrochloric acid as prisms, darkens at 210°, m. 237° (decomp.). —HYDRIODIDE, B·HI, cryst. darkens at 230°, m. p. 240° (decomp.). —SULPHATE, needles. —NITRATE, tablets. —PICRATE, crystalline. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$, m. p. 230° to 233° (decomp.). —METHOMETHYLSULPHATE, $B(CH_3)_2SO_4$, cryst. as prisms from water, darkens at 150°, m. p. 245° to 248° (decomp.). —METHIODIDE, $B \cdot CH_3I$, striated prisms, m. p. 233° to 235° (decomp.). —METHOCHLORIDE (22), $B \cdot CH_3Cl + 2H_2O$, cryst. as colorless prisms from methanol, m. p. 233° (decomp.).

METHYLPSEUDOANHYDROCRYPTOPINE (9): $B = C_{23}H_{23}O_6N$, prepared by exhaustive methylation of isoanhydrocryptopine; amorphous. —HYDRIODIDE, B·HI, cryst. as chalky powder from water, m. p. indefinite.

DIHYDROISOANHYDROCRYPTOPINE (22): $C_{21}H_{23}O_4N$, obtained by sodium amalgam reduction of isoanhydrocryptopine; amorphous. —HYDROCHLORIDE, cryst. as prisms from dil. hydrochloric acid, darkens at 210°, m. at 215° to 218° (decomp.).

DIHYDROMETHYLISOANHYDROCRYPTOPINE-A (22): $C_{22}H_{25}O_4N$, both the A- and B-isomers are obtained by sodium amalgam reduction of isoanhydrocryptopine; cryst. from methanol as needles, sinter at 105° and change to the B-isomer, melting at 121° to 122°. B-ISOMER, $C_{22}H_{25}O_4N$, cryst. as prisms (measurements given) from methanol, m. p. 121° to 122°. —HYDROCHLORIDE, cryst. as 6-sided prisms from water. —METHOMETHYLSULPHATE, cryst. from water or methanol, m. p. 202°. Methyl alcoholic KOH reacts to give trimethylamine and a black substance. —METHIODIDE, cryst. from alcohol as circular warts, m. p. 215° to 217°.

PSEUDODIHYDROMETHYLISOANHYDROCRYPTOPINE (22): $C_{22}H_{25}O_4N$, obtained by reducing isoanhydrocryptopine methochloride or by boiling dihydromethylisoanhydrocryptopine with dilute hydrochloric acid. Cryst. as needles from methanol or acetone, m. p. 140° to 141°. —METHOMETHYLSULPHATE, cryst. from water or methanol as groups of colorless needles, m. p. 188° to 190°.

BASE: $C_{22}H_{25}O_4N$, isomeric with dihydromethylisoanhydrocryptopine and pseudodihydromethylisoanhydrocryptopine, obtained as a by-product of the reduction of the latter with sodium amalgam. Cryst. from methanol as needles, m. p. 168° to 170°.

TETRAHYDROMETHYLISOANHYDROCRYPTOPINE (22): $C_{22}H_{27}O_4N$, a by-product of sodium amalgam reduction of pseudodihydromethylisoanhydrocryptopine, amorphous. —METHIODIDE, cryst. as flat plates from methanol, m. p. 188° to 190°.

ISOCRYPTOPIDENE-A (22): $C_{20}H_{20}O_4$, obtained by sodium amalgam reduction of dihydromethylisoanhydrocryptopine methomethylsulphate (at 30°), and of pseudodihydromethylisoanhydrocryptopine, and of the methomethylsulphate of the latter (at 50°). Cryst. from methanol or acetone as striated prisms, m. p. 166° to 167°. ISOCRYPTOPIDENE-B (22): $C_{20}H_{20}O_4$, obtained by the sodium amalgam reduction of dihydromethylisoanhydrocryptopine. Cryst. as needles from methanol, or 70% acetic acid, m. p. 108°.

KETOHYDROXYDIHYDROISOCRYPTOPIDENIC ACID (22): $C_{20}H_{20}O_8$, obtained by permanganate oxidation of isocryptopidene-B. Cryst. from methanol, m. p. 227°.

EPICRYPTOPINE-A (9): $B=C_{21}H_{23}O_5N$. The two isomers, A and B, are obtained by boiling anhydrocryptopine with conc. hydrochloric acid. Isomer-A results also from the action of dil. hydrochloric acid on the B-isomer. Cryst. as prisms from methanol or benzene, m. p. 210° to 212°. —HYDROCHLORIDE, $B{\cdot}HCl$, sl. sol. in dil. hydrochloric acid. —HYDRIODIDE, $B{\cdot}HI$, cryst. from water, darkens at 210°, m. at 230° to 232° (decomp.). —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6$, ochreous. —MERCURICHLORIDE, crystalline. —PICRATE, resinous. —ACETYL DERIVATIVE, $C_{23}H_{25}O_6N$, crystals, darkening at 285° and melting at 290°. EPICRYPTOPINE-B (9): $C_{21}H_{23}O_5N$, obtained with the A-isomer as above, or from the A-isomer by heating with methanol at 110°; amorphous. —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6$. —ACETYL DERIVATIVE, $C_{23}H_{25}O_6N$, cryst., darkens at 280°, m. p. 290° to 295°. —EPICRYPTOPINE-C (9): $C_{21}H_{23}O_5N$, obtained from the A-isomer by boiling with ethyl acetate or acetic acid. Cryst. from ether as nodules of m. p. 165° to 167°. —ACETYL DERIVATIVE, apparently the same as that of the A- and B-isomers. —ACETATE, $B{\cdot}C_2H_4O_2$, cryst. of m. p. 184° to 185°.

EPICRYPTOPIRUBIN (9). —CHLORIDE, $C_{21}H_{22}O_4NCl$, formed by the action of phosphorous oxychloride on epicryptopine-A; scarlet cryst. from water, m. p. 220° to 223° (decomp.). —NITRATE, cryst. as vermillion flat striated prisms. —IODIDE, orange-red prisms from methanol. —PLATINICHLORIDE, maroon powder, decomp. at 205° to 210°. —PICRATE, orange cryst. DEHYDROEPICRYPTOPIRUBIN CHLORIDE (?) (9): $C_{21}H_{20}O_4NCl$, a by-product in the preparation of epicryptopine hydrochloride; red powder, m. p. 150° to 155° (decomp.). –Hydroxide, $C_{21}H_{21}O_5N$, prepared by the action of sodium hydroxide on epicryptopirubin chloride; reddish-black crystalline powder. BASE (9), $C_{21}H_{19}O_6N$, obtained as a by-product of the action of alkali on epicryptopirubin chloride, and in the preparation of epicryptopine hydrochloride; brown cryst. powder. KETOISOEPICRYPTOPIRUBIN (9), $C_{21}H_{19}O_5N$, obtained by the action of phosphorous oxychloride on ketoanhydrocryptopine. Cryst. as prisms from dil. acetic acid or alcohol, darkens above 210°, m. p. ca. 235° to 240°; –Hydrochloride, crimson cryst. precip.; –Platinichloride, crimson precipitate; –Aurichloride, maroon precipitate.

OXYCRYPTOPINE (41): $C_{21}H_{21}O_6N+6H_2O$, obtained by oxidation of cryptopine with mercuric acetate; white prisms, sol. in water, m. p. (hydrated) 98° to 99°, (anhydrous) 180° to 187°. —NITRATE, $C_{21}H_{21}O_6N{\cdot}HNO_3$, thick colorless cryst. from water; does not form an oxime or o-phenylenediamine. DIHYDROOXYCRYPTOPINE (41), $C_{21}H_{23}O_6N$, obtained by aluminum amalgam reduction of oxycryptopine. Cryst. as warts from dil. alcohol, m. p. 184°; –Aurichloride, amorphous, m. p. 191° to 192° (decomp.). TETRAHYDROOXYCRYPTOPINE (41), $C_{21}H_{25}O_6N$, obtained by sodium amalgam reduction of oxycryptopine; cryst. from ether as white warts, from alcohol as scales, m. p. 223°; –Aurichloride, amorphous, m. p. 160° (decomp.).

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PROTOPINE

Protopine was discovered in opium in 1871 by Hesse (1) (2). It occurs also in a wide variety of papaverlike plants, as listed below, and has been described under the names Fumarine (3) and Macleyine (4) (5). The separation of protopine from opium as carried out by Hesse is exceedingly laborious, and the alkaloid can be more advantageously obtained from the root of *Dicentra spectabilis* or from *Diclytra spectabilis*, in which Danckwortt (6) and Gadamer (7) found it to be present to the extent of nearly one per cent. The protopine

is extracted from the pulverized roots directly by alcohol, and in contrast to the crude product obtained from opium, can be easily purified. The wide distribution of protopine is evident from the sources listed in the following table.

Corydalis cava	Gadamer and Brückhausen (8) (9).
Dicentra spectabilis	Danckwortt (6), Gadamer (7).
Diclytra spectabilis	Gadamer (7), Battandier (10).
Chelidonium majus	Gadamer (7), Wintgen (11), Kratzmann (12) (13), Schmidt (14), Selle (15) (16), König (17).
Diclytra formosa	Battandier (10).
Corydalis vernyi	Makoshi (18).
Corydalis decumbens	Osada (19).
Corydalis solida	Heyl (20).
Corydalis ambigua	Makoshi (18).
Dicentra cucullaria	Fischer and Söll (21).
Dicentra formosa	Heyl (22).
Dicentra pusilla	Asahina (23).
Papaver somniferum	Hesse (1).
Argemone mexicana	Schlotterbeck (24).
Eschscholtzia californica	Schmidt (14), Fischer (25), Fischer and Tweeden (26).
Sanguinaria canadensis	Fischer (27), Schmidt (14), König and Tietz (28), König (29), Kozniewski (30).
Macleya cordata (*Bocconia cordata*).	Murrill and Schlotterbeck (3), Hopfgartner (32), Eijkman (33), Honda (5), Schlotterbeck (34).
Adlumia cirrhosa	Eijkman (33), Selle (15), König and Tietz (28), Schmidt (14), Schlotterbeck (3) (35) (36).
Glaucium luteum	Schmidt (14), Fischer (37).
Fumaria officinalis	Murrill and Schlotterbeck (3).
Stylophorum diphyllum	Schmidt (14), Schlotterbeck and Watkins (38).
Bocconia frutescens	Battandier (39).
Glaucium corniculatum	Battandier (39).

The empirical formula $C_{20}H_{19}O_5N$ for protopine was established by Hesse (2), and has been confirmed by numerous other investigators. Protopine forms colorless monoclinic prisms (40) and melts at 207° (6) (41), (208° corr. (3)). It is soluble in alcohol (1 part in 900) or ether (1 part in 1,000), fairly soluble in chloroform (1 part in 15) (4), sparingly soluble in ethyl acetate, carbon disulphide, benzene, or petroleum ether (32). The base may be crystallized from alcohol, ether, or chloroform, the most suitable medium being a mixture of alcohol and chloroform (6) (32). Protopine, like cryptopine, is optically inactive (32). The physiological action of the alkaloid has been studied by von Engel (42) and others (43) (44).

A number of color tests which have been described for protopine are tabulated as follow:

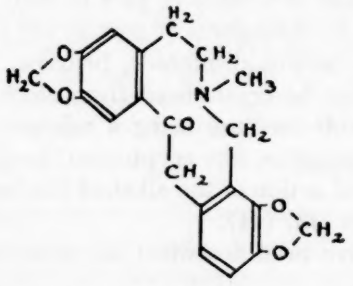
Protopine: Color reactions

Reagent	Reaction	Observer
Conc. H_2SO_4	Yellow turning blue-violet then green	Danckwortt (6), Eijkman (33).
Fröhde's reagent	Olive turning violet then green	Danckwortt (6).
Molybdic acid in conc. H_2SO_4	Purple or blue	Eijkman (33).
$K_2Cr_2O_7$ in conc. H_2SO_4	Intense blue	Do. (33).
$FeSO_4$ in conc. H_2SO_4	Blue-violet	Do. (33).
Acetic acid and H_2SO_4	Deep blue-violet	Perkin (45).
Erdmann's reagent	Violet	Danckwortt (table) (6).
Mandelin's reagent	do	Danckwortt (6).

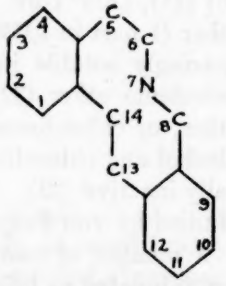
Microchemical reactions are described by V. Itallie and Toorenburg (46). The absorption spectrum was studied by Dobbie and Fox (47) and Kitasato (48), and is similar to the spectra of the isoquinoline alkaloids.

Protopine contains no methoxyl groups (32); four of the oxygens are linked in the form of two methylenedioxyl groups (6). The nitrogen atom, which is tertiary and forms part of a ring, carries a methyl group (6). Protopine is unaffected by catalytic reduction processes, and therefore contains no ethylenic linkage (6). Protopine does not behave as though it contained a hydroxyl group (6), but can be reduced to a secondary alcohol (6) (49); the fifth oxygen atom is probably present in a carbonyl group, although the alkaloid is indifferent to the Grignard compound (6) (49), and the reagents which ordinarily serve to identify ketones.

From the investigations of Danckwortt (6) (50) it became apparent that protopine was closely related to cryptopine, and differed from the latter only in containing a methylenedioxyl group in place of the two methoxyl groups of cryptopine. Perkin (45) extended the study of protopine and showed the complete analogy of its transformations and degradations with those of cryptopine. Protopine is represented by the following structural formula.



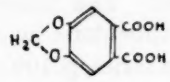
I. Protopine



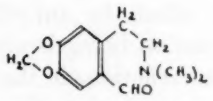
Numbering System

Oxidation of protopine (6) gives hydrastic acid, which must be formed from that part of the protopine molecule corresponding to the dimethoxylated nucleus in cryptopine. The position of nitrogen with respect to the ring yielding hydrastic acid was shown by the results of oxidation of anhydrotetrahydromethylprotopine (V),

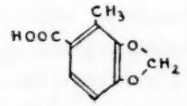
where in addition to methylpiperonylic acid, N-methylhydrastinine (dimethylaminoethyl-4, 5-methylenedioxybenzaldehyde) was obtained (9).



Hydrastic Acid



N-Methylhydrastinine

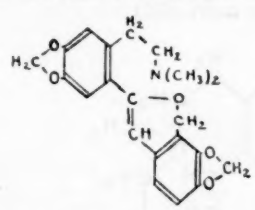


Methylpiperonylic Acid

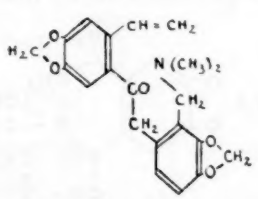
Ozonization of anhydrotetrahydromethylprotopine (V) yielded methylpiperonal. The appearance of methylpiperonal and its acid shows the presence of a second aromatic nucleus carrying a methylenedioxyl group.

Gadamer and Kollnar (49) obtained oxyprotopine by oxidation of protopine with mercuric acetate. Reduction of oxyprotopine with sodium amalgam yields tetrahydrooxyprotopine, whereas zinc and acid or aluminum amalgam reduction gives two different bases. Legerlotz (51) considers the mercuric acetate oxidation an argument against the Perkin protopine formula.

Protopine suffers degradation parallel to that of cryptopine when it is heated in the form of the methomethylsulphate with alkali (6) (45). The isomeric methylprotopines (α-and γ-) thus prepared are considered to result from ring scission in two ways (45).

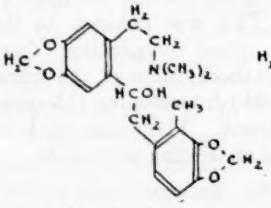


II. α-Methylprotopine

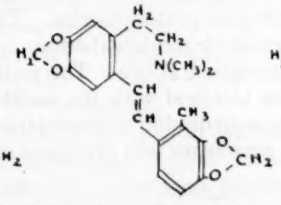


III. γ-Methylprotopine

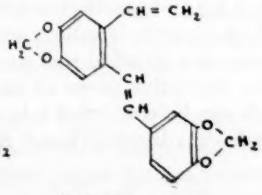
The Emde degradation (9) of protopine methomethylsulphate with sodium amalgam proceeds to a certain extent like that of cryptopine. The 10-membered ring is opened reductively, with formation of tetrahydromethylprotopine, which can be dehydrated to anhydrotetrahydromethylprotopine, whose oxidative degradation was mentioned above. Exhaustive methylation of anhydrotetrahydromethylprotopine results in the nitrogen-free propidene. This substance oxidizes to hydrastic acid, methyl piperonal and methylpiperonylic acid (19).



IV. Tetrahydromethylprotopine



V. Anhydrotetrahydromethylprotopine

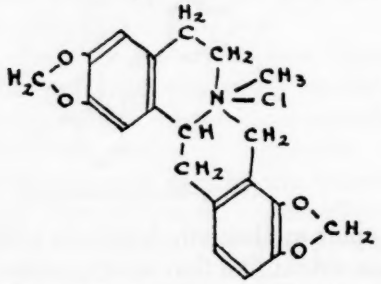


VI. Propidene

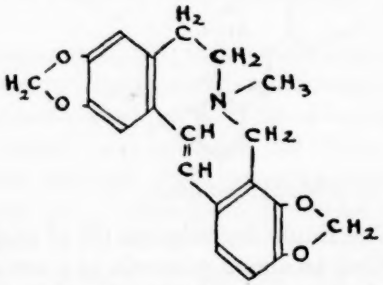
In analogy with cryptopine, protopine closes a nitrogen-carbon linkage when heated with phosphorous oxychloride, forming isoprotopine chloride (45). (See also Danckwortt (6).) This quaternary chloride is converted by alkali to anhydroprotopine. The latter substance gives epiprotopine on being heated with hydrochloric acid (45) (compare the analogous reactions in the cryptopine series, p. 109).

Isoprotopine chloride loses methyl chloride when heated under reduced pressure, yielding 2, 3, 9, 10-bismethylenedioxydihydroprotoberberine, whose tetrahydro derivative has been synthesized (52).

Dihydroprotopine is obtained through reduction of protopine with sodium amalgam (6) (49), and undergoes ring closure on treatment with benzoyl chloride (6) or phosphorous oxychloride (19) to isodihydroprotopine chloride. The last named substance has also been prepared by direct reduction of protopine with zinc and hydrochloric acid (49) and other agents (49) (52). Through the action of alkali, isodihydroprotopine chloride suffers ring scission (19), (52), (60), with formation of anhydrodihydroprotopine-A (52) and -B (19) both of which degrade to methylisoanhydrodihydroprotopine. This degradation product has been oxidized to a substance resembling hydrastal (19). Anhydrodihydroprotopine-A is converted back to isodihydroprotopine chloride by heating with hydrochloric acid (52).



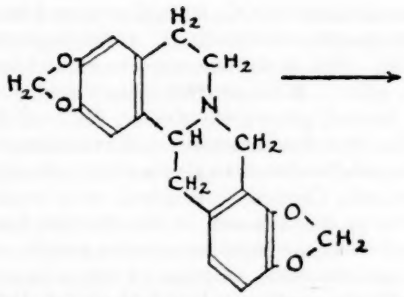
VII. Isodihydroprotopine Chloride



VIII. Anhydrodihydroprotopine-A

Anhydrodihydroprotopine-A has been synthesized, and forms a step in the total synthesis of protopine (52), which is completely analogous to the cryptopine synthesis described on page 113.

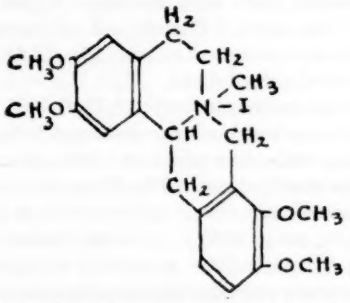
N-β-Piperonylethyl-3,4-methylenedioxyhomophthalamic acid, from condensation of N-β-piperonylethylamine and 3,4-methylenedioxyphthalic anhydride, was treated as the methyl ester with phosphorous oxychloride, closing two rings to form 2,3,9,10-bismethylenedioxyoxyprotoberberine. This was reduced to the 2,3,9,10-bismethylenedioxytetrahydroprotoberberine whose preparation from isoprotopine chloride was mentioned above. The methochlorides of the tetrahydro derivative prove to be identical with the isodihydroprotopine chlorides, which can be converted into anhydrodihydroprotopine-A. The amine oxide of anhydrodihydroprotopine-A rearranges into protopine on heating with acids.



Isodihydroprotopine chloride
↓
Anhydrodihydroprotopine-A
↓
Amine oxide
↓
Protopine

IX. bis-Methylenedioxytetrahydroprotoberberine

The relationship between protopine and the alkaloid palmatine was shown by the conversion of protopine into tetrahydropalmatine by Osada (19). Isodihydroprotopine chloride was treated with phloroglucinol and sulphuric acid, which converted the methylenedioxyl groups into four hydroxyls, which were then methylated. The methiodide of tetrahydropalmatine was obtained.



X. Tetrahydropalmatine Methiodide

Descriptive Part (Protopine)

PROTOPINE: B=$C_{20}H_{19}O_5N$. —HYDROCHLORIDE (7) (8), B·HCl (¼H_2O) (32), sol. in cold water (1:140) (33). —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6+4H_2O$ (18); (+$2H_2O$) (11) (33); yellow crystalline powder. —AURICHLORIDE, B·$HAuCl_4$ (11), crystal warts from alcohol containing HCl. —HYDRIODIDE (33), B·HI, cryst. spheres, slightly sol. in hot water and hot alcohol. —NITRATE (32), B·HNO_3, slightly sol. in water (1:714 at 7°), sol. in hot water or alcohol; used for purification of the alkaloid. —NEUTRAL SULPHATE, colorless needles. —CHROMATE, B·$H_2Cr_2O_7$, orange prisms. —THIOCYANATE, star-grouped needles. —ACETATE, grouped needles. —OXALATE, —TARTRATE, —PICRATE, —BENZOATE (m. p. 166°), —MERCURIODIDE, are known (33).

PROTOPINE METHOMETHYLSULPHATE (6) (50) (45):B·$(CH_3)_2SO_4$, cryst. in prismatic needles from dilute alcohol; darkens at 240°, m. p. 252° (decomp.) (9). It is sol. in hot water and forms a jelly on cooling; cryst. as prism clusters from methanol (45). PROTOPINE METHIODIDE (6) (45): B·CH_3I, prep. by treating the methomethylsulphate with KI. Slightly sol. in water, cryst. from methanol as star-grouped twinned crystals. Two kinds of crystals have been noted (32). Darkens at 210°, m. at 217°. (decomp.).

DIHYDROPROTOPINE (Hydroprotopine) (6) (32) (49): $C_{20}H_{21}O_5N$ (+½C_2H_5OH), prep. by reduction of protopine according to the method of Kostanecki (53), or with sodium amalgam (6) (32). Cryst. as colorless plates from a mixture of alcohol and ether, m. p. 120°; solvent-free, m. p. 151° to 152°. —HYDROCHLORIDE (6), cryst. as plates from water or as needles from alcohol.

α-METHYLPROTOPINE (45) (Protopine methine (6)): $C_{21}H_{21}O_5N$, prepared from protopine methomethylsulphate by heating with alcoholic KOH. Cryst. in prisms from ethyl acetate, m. p. 144° to 145° (45). Sol. in acetone, benzene, chloroform, slightly sol. in ether; insol. petroleum ether. With acetic-sulphuric acid mixture, it gives a violet color; conc. HCl (heated) gives a violet color; HCl and KI gives a precipitate. —METHIODIDE (6), cryst. from acetone. —METHOMETHYLSULPHATE (6), crystalline; Hofmann degradation failed to give a cryst. nitrogen-free product (6). γ-METHYLPROTOPINE (45), $C_{21}H_{21}O_5N$, prepared from protopine methomethylsulphate, separated from the α-isomer in the filtrates from ethyl acetate recrystallization. It cryst. from methanol as granular powder, m. p. 110° to 112°; the other properties are the same as those of the α-isomer. —PLATINICHLORIDE, $B_2 \cdot H_2PtCl_6$, gelatinous cryst. precip.; darkens at 180°, decomp. at 230°.

ISOPROTOPINE CHLORIDE (45): $C_{20}H_{18}O_4NCl$, prep. by digesting protopine with phosphorous oxychloride. Pale ochreous needles from water; darkens at 175°, melts at 215° (decomp.). Danckwortt (6), by the action of benzoyl chloride on protopine, obtained a product probably identical with isoprotopine chloride. ISOPROTOPINE DISULPHATE (45), $C_{20}H_{18}O_4N \cdot HSO_4 \cdot H_2SO_4$, obtained by heating the chloride with acetic-sulphuric acid mixture. Cryst. precip. which darkens at 180°, melts at 247° (decomp.). Slightly sol. in water, cryst. from water as gelatinous needles. ISOPROTOPINE SULPHATE (45), $(C_{20}H_{18}O_4N)_2SO_4$ (?). obtained by action of ammonia on the disulphate.

α-ISODIHYDROPROTOPINE CHLORIDE (52): $C_{20}H_{20}O_4NCl$, obtained by Clemmensen reduction of protopine, or by aluminum amalgam reduction (49), or by electrolytic or sodium amalgam reduction of isoprotopine chloride (52). Cryst. from conc. aqueous solution as stout prisms. The HYDRATE melts ca. 90°. It becomes anhydrous at 100°, and the anhydrous salt darkens at 155° and melts at 175° (decomp.). (Osada (19), m. p. 215°.) β-ISODIHYDROPROTOPINE CHLORIDE (52), $C_{20}H_{20}O_4NCl$, obtained by electrolytic or sodium amalgam reduction of isoprotopine chloride, or by heating anhydrodihydroprotopine-A with dil. HCl. Cryst. as colorless plates from hot water, decomp. at 270°. "QUATERNARY ANHYDROBASE" (6), $C_{20}H_{20}O_4NCl + 5H_2O$, obtained by the action of benzoyl chloride on dihydroprotopine. It is probably identical with β-isodihydroprotopine chloride. Cryst. from water, m. p. 275° (decomp.). –Aurichloride, $C_{20}H_{20}O_4NCl \cdot AuCl_3$, red-brown needles.

ANHYDROPROTOPINE (45): $C_{20}H_{17}O_4N$, obtained by boiling isoprotopine chloride with alcoholic KOH. Pale yellow prisms from methanol, m. p. 114° to 115°; sol. in acids with deep yellow color. Acetic-sulphuric acid mixture gives a wine color. The base is converted to a resin by hot dil. HCl. —HYDROCHLORIDE, cryst. from water. The ACETATE is hydrolyzed in water.

EPIPROTOPINE (45): obtained by boiling anhydroprotopine with conc. HCl, isolated as the HYDROCHLORIDE (cryst. slimy precip.). The base, liberated by ammonia, gives a fluorescent solution in ether from which crusts separate on evaporation.

ANHYDRODIHYDROPROTOPINE-A (52) (α) (19): $C_{20}H_{19}O_4N$, prepared by the action of silver hydroxide on α- or β-isodihydroprotopine chlorides. It cryst. as needles from acetone, m. p. 118° to 120° (52). On heating with dil. HCl it gives β-isodihydroprotopine chloride. —METHIODIDE (6) (19), m. p. 232°. —METHOMETHYLSULPHATE (19), yellow, m. p. 176° to 177°. ANHYDRODIHYDROPROTOPINE OXIDE (52), $C_{20}H_{19}O_5N$, obtained by the action of perbenzoic acid on anhydrodihydroprotopine-A. It cryst. as colorless needles from water, m. p. 140° (decomp.). Heating with acetic acid and conc. HCl gives protopine. —HYDROCHLORIDE, cryst. as colorless needles from water, m. p. 221° (decomp.). ANHYDRODIHYDROPROTOPINE-B (19), $C_{20}H_{19}O_4N$, obtained together with the A-isomer by

the action of alcoholic KOH on isodihydroprotopine chloride, m. p. 145°. —METHIODIDE, m. p. 236°. Danckwortt (6) in 1912 obtained in the same way a "tertiary anhydro-base," $C_{20}H_{19}O_4N$, which cryst. as long needles of m. p. 145°; –Methiodide, m. p. 230° (decomp.). This compound is evidently the same as that studied by Osada (19).

METHYLISOANHYDRODIHYDROPROTOPINE (19): $C_{21}H_{21}O_4N$, obtained by the action of alkali on the methiodide of anhydrodihydroprotopines -A and -B; white cryst. of m. p. 105°. Oxidation by permanganate gives a substance (m. p. 79°) resembling hydrastal. Danckwortt (6) obtained in 1912 by a similar degradation of protopine a crystalline "methine" of m. p. 112°, which was fluorescent in ether and added bromine. —METHIODIDE (6), needles. —METHOMETHYLSULPHATE (6), gives with sodium hydroxide a resinous vinyl derivative.

TETRAHYDROMETHYLPROTOPINE (9): $C_{21}H_{25}O_5N$, obtained by the reduction of protopine methomethylsulphate with sodium amalgam, m. p. 114° to 115°. —HYDROCHLORIDE, cryst. in plates. BASE (9), m. p. 194°, obtained in 10% yield in reduction of protopine methomethylsulphate by sodium amalgam.

ANHYDROTETRAHYDROMETHYLPROTOPINE (9): $C_{21}H_{23}O_4N$, obtained by the action of acetyl chloride on tetrahydromethylprotopine. Cryst. as needles from methanol, m. p. 50° to 60°, solvent-free, m. p. 84°. It cryst. also from ether. —METHOMETHYLSULPHATE (37), colorless cryst. of m. p. 236°.

PROPIDENE (19): $C_{19}H_{16}O_4$, m. p. 106°.

OXYPROTOPINE (49): $B=C_{20}H_{17}O_6N$, obtained by action of mercuric acetate in acetic acid on protopine (75% yield). Pale yellow cryst. of m. p. 225°. It cryst. from dil. acid by addition of ammonia. It does not acetylate, nor react with phenyl magnesium bromide. The hydrochloride does not reduce by the method of Paal and Skita, nor electrolytically. —PLATINICHLORIDE, $B_2{\cdot}H_2PtCl_6 + 4H_2O$, amorphous, m. p. 222°. —HYDROBROMIDE, B·HBr, yellow cryst. warts, slightly sol. in water, m. p. 274° to 275°. —NITRATE, B·HNO_3, white plates, sl. sol. water, m. p. 274° to 275° (decomp.). MERCURIZED BASE, $C_{20}H_{18}O_5NHCl{\cdot}HgCl$, amorphous. BASE, m. p. 140° to 150° and BASE, m. p. 255° to 256°, obtained by sodium amalgam reduction. BASE, m. p. 222° to 223°, by zinc and acid reduction. BASE, m. p. 202° to 203° by aluminum amalgam reduction.

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PAPAVERAMINE

Papaveramine, $C_{21}H_{25}O_6N$, was discovered by Hesse in 1886 (1) (2) as an impurity accompanying papaverine. It was separated from papaverine by converting the mixture to the acid oxalate, from which potassium thiocyanate precipitated papaverine thiocyanate nearly completely. From the filtrate, after separation of a small amount more of papaverine binoxalate, the new base could be isolated (3).[75]

Papaveramine crystallizes from alcohol or ether in colorless thin prisms of melting point 128° to 129°. It is very soluble in chloroform, fairly soluble in alcohol or ether, slightly soluble in ammonia, but insoluble in water or alkali. It dissolves with difficulty in acetic acid. It is apparently a very weak base and does not neutralize acids completely. With concentrated sulphuric acid the alkaloid gives an

[75] Pictet and Kramers (4) carried out a similar purification of papaverine to determine the nature of the impurity present which gives the strong color reaction of commercial papaverine with sulphuric acid. Cryptopine was found in this case, to the extent of about 4%. It resembles Hesse's papaveramine in giving an intense blue-violet color with concentrated sulphuric acid, but in all other respects is quite dissimilar.

intensely colored blue-violet solution. Concerning the structure or properties of papaveramine nothing further is known.

PAPAVERAMINE HYDROCHLORIDE is very soluble in water, and remains as a sirup on evaporation of the solution; from this, concentric-grouped short prisms separate on addition of absolute alcohol. With chloroplatinic acid it yields an amorphous PLATINICHLORIDE $(C_{21}H_{25}O_6N \cdot HCl)_2PtCl_4 + 3H_2O$, which is soluble with difficulty in cold water.

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LANTHOPINE

Lanthopine, $C_{23}H_{25}O_4N$, was separated from the black mother liquors of opium by Hesse in 1870 (1) (2). It usually crystallizes from chloroform as a white powder, consisting of microscopic prisms, but may also be obtained as long prisms grouped in a fanlike structure. It is almost insoluble in alcohol, ether, or ligroin, fairly soluble in chloroform. Lanthopine is a very weak base and does not affect red litmus paper. It does not neutralize acetic acid, and its hydrochloride is hydrolyzed to a considerable extent. The base apparently contains a phenolic group, for it is precipitated from its salts by alkali or lime water, and dissolves in an excess of the reagent. From the alkaline solution it is again precipitated by ammonium chloride. It gives, however, no ferric chloride reaction. The pure base dissolves colorless in concentrated sulphuric acid.

Lanthopine crystallizes anhydrous. On heating, the crystals begin to color at about 190°, and by rapid heating can be made to melt at about 200° before decomposition is complete. Machiguchi (3) reports lanthopine as melting at 141° to 145°.

LANTHOPINE HYDROCHLORIDE: $C_{23}H_{25}O_4N \cdot HCl + 6H_2O$, is prepared by dissolving the base in a slight excess of dilute hydrochloric acid. It forms hairlike crystals, grouped in jellylike masses. It is soluble in warm water and tastes bitter. With chloroplatinic acid it yields the PLATINICHLORIDE $(C_{23}H_{25}O_4N \cdot HCl)_2PtCl_4 + H_2O$, as a lemon-yellow crystalline powder (1). LANTHOPINE HYDRIODIDE precipitates as a jellylike mass when potassium iodide solution is added to a solution of lanthopine oxalate. It dissolves in boiling water, but separates again as a jelly on cooling. LANTHOPINE MERCURIODIDE is a white amorphous precipitate, soluble in hot water or alcohol (1). LANTHOPINE SULPHATE crystallizes in exceedingly thin needles, resembling narceine (1). LANTHOPINE ACID TARTRATE consists of colorless fine prisms, very soluble in water or alcohol (2). LANTHOPINE BINOXALATE forms jellylike masses which soon become crystalline; very soluble in water or alcohol (2).

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MECONIDINE

Meconidine, $C_{21}H_{23}O_4N$, was discovered by Hesse (1) in 1870. It was isolated by ether extraction of the clear mother liquor obtained when an aqueous extract of opium was precipitated with soda. It forms a portion of the so-called Porphyroxin of Merck (2). Meconidine can not be obtained from the mother liquors from the Robinson-Gregory process, since it is destroyed by the reagents used (3).

Meconidine was separated as a brownish yellow amorphous mass, of m. p. 58°; very soluble in alcohol, ether, ligroin, chloroform, and acetone. The alcoholic solution reacts basic to litmus. The base neutralizes acids, but is decomposed by excess of mineral acid to give intensely colored solutions. It is soluble in alkalies. Since neither the base nor its salts was obtained crystalline, its existence as a pure alkaloid may well be doubted. Machiguchi (4) reports the presence of meconidine in Japanese opium.

MECONIDINE HYDRIODIDE, colorless amorphous precipitate, very soluble in water or alcohol (1). MECONIDINE AURICHLORIDE, yellow amorphous precipitate (1). MECONIDINE PLATINICHLORIDE, yellow amorphous precipitate $(C_{21}H_{23}O_4N\cdot HCl)_2PtCl_4$ (1), $+2H_2O$ (4). MECONIDINE MERCURICHLORIDE, a white amorphous precipitate which turns pink with excess of HCl (1)

Bibliography (Meconidine)

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RHŒADINE

The alkaloid rhœadine, $C_{21}H_{21}O_6N$, was discovered by Hesse (1) in the seed-capsules and other parts of *Papaver rhœas* L., the scarlet wild poppy or corn poppy. On the evidence of the very sensitive color reaction of rhœadine with mineral acids, Hesse believed to have detected rhœadine in opium (2) but in a later investigation stated that the color reaction was due to another unidentified alkaloid of opium (3). Whether rhœadine should be considered as an opium alkaloid is not certain.

Hesse obtained rhœadine by extracting the finely ground plants of *Papaver rhœas* with warm water. The aqueous extract was concentrated at a moderate temperature, treated with an excess of sodium carbonate, and shaken out exhaustively with ether. The ether was extracted with sodium bitartrate solution, and the rhœadine precipitated from the latter by ammonia as a grayish amorphous mass which rapidly became crystalline. Boiling the crystalline precipitate with alcohol removed coloring matter and traces of another alkaloid, believed to be thebaine. Further purification was accomplished by decolorizing an acetic acid solution of the base with charcoal and again precipitating with ammonia (2).

Pavesi (4) isolated rhœadine by extracting the pulverized *Papaver rhœas* with milk of lime, drying the entire extract, and boiling out with ether. The base was then converted to the bitartrate as in the method of Hesse.

Rhœadine crystallizes in fine white prisms or starlike groups of needles of m. p. 232° (2), (thin double-refracting needles which brown at 238° to 240° and melt at 245° to 247°) (4). It sublimes readily in an indifferent atmosphere and is deposited as long white prisms. It is almost insoluble in ether, benzene, chloroform, alcohol, water, ammonia, soda solution, or limewater. One part of the base dissolves in 1,280 parts of ether at 18° (2), or in 1,100 parts of 80% alcohol (3). Pavesi (4) reports that 1.5 g. of the base dissolves in 1 liter of alcohol, but that it is somewhat more soluble in amyl alcohol or benzol.

Rhœadine is apparently a very weak base. In alcoholic solution it scarcely turns red litmus. It dissolves in acids but is changed rapidly by them; in cold acetic acid it is fairly stable, but is decomposed on warming. Sodium or potassium hydroxide precipitates it from cold acetic acid in the form of fine white prisms, insoluble in excess of alkali (2) (3). The base and its salts are tasteless and not poisonous (2).

Hesse (2) describes the following salts of rhœadine: RHŒADINE TANNATE, a white amorphous precipitate. RHŒADINE MERCURICHLORIDE, a white precipitate, readily soluble in water. RHŒADINE MERCURIODIDE, a pale yellow insoluble precipitate. RHŒADINE AURICHLORIDE, a yellow curdy precipitate, sparingly soluble in acids. RHŒADINE PLATINICHLORIDE, a yellow, amorphous, fairly soluble precipitate having the composition (4) $(C_{21}H_{21}O_6NHCl)_2PtCl_4+2H_2O$. RHŒADINE HYDRIODIDE precipitates when potassium iodide is added to rhœadine in acetic acid solution. It consists of white microscopic prisms, soluble in hot water, from which it separates as concentric-grouped prisms on cooling. It has the composition $C_{21}H_{21}O_6N\cdot HI+2H_2O$. About half of the hydrate water is lost on drying in a desiccator; on drying in the air, the salt shrinks down to a noncrystalline mass (3).

Strong acids, especially hydrochloric or sulphuric acids, in moderate concentration dissolve rhœadine with a purple-red color which is so intense as to permit the detection of the alkaloid in a dilution of 1:800,000. In this reaction only about 5% or less of the rhœadine is converted to the colored material; the remainder consists of a new isomeric base, rhœagenine, which is precipitated by the addition of ammonia after the colored substance has been removed from the acid solution with charcoal.

Rhœagenine crystallizes from hot alcohol in small white prisms or rectangular leaflets, which are solvent-free and have the composition $C_{21}H_{21}O_6N$. It is sparingly soluble in ether (1:1,800), alcohol (1:1,500), water, or ammonia. It is soluble in acids and stable toward them with the exception of concentrated nitric acid, which decomposes it with yellow color. Rhœagenine is a strong base, and forms neutral salts. In alcoholic solution it turns litmus blue. The base is tasteless, but its salts have a bitter taste. Rhœagenine differs form rhœadine notably in its refractive index (4) and in not being sublimable. It

melts at 223° (2) (235° to 237.5°) (4) to a colorless liquid which rapidly turns brown and decomposes.

RHŒAGENINE HYDROCHLORIDE, colorless concentric-grouped needles, soluble in water or alcohol, sparingly soluble in sodium chloride solution (3). —MERCURICHLORIDE, is a white amorphous precipitate, soluble in water or acids (2). —MERCURIODIDE, is a pale yellow precipitate almost insoluble in dilute acids (2). —AURICHLORIDE is an amorphous yellow powder (2). —PLATINICHLORIDE $(C_{21}H_{21}O_6N \cdot HCl)_2PtCl_4$, is an amorphous precipitate. RHŒAGENINE HYDRIODIDE, $C_{21}H_{21}O_6N \cdot HI$, short thick prisms from water (3). RHŒAGENINE NITRATE is formed as large glassy prisms when the base is dissolved in warm dilute nitric acid (3). RHŒAGENINE SULPHATE is obtained as an amorphous mass when a solution of rhœagenine in the calculated amount of sulphuric acid is evaporated. The salt is very soluble in water, sparingly so in alcohol, and reacts neutral; it gives no color with ferric chloride (2). RHŒAGENINE CHROMATE is a yellow precipitate, soluble with difficulty in water (2). RHŒAGENINE OXALATE is obtained by dissolving the base in an excess of oxalic acid, removing the excess acid with lime water, and concentrating. A small amount of the free base first separates, and then the oxalate as thin colorless prisms (3). RHŒAGENINE TRIBROMIDE, $C_{21}H_{21}O_6N \cdot Br_3$, is described by Pavesi (4).

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APOREINE

Aporeine, $C_{18}H_{16}O_2N$, was discovered in 1905 by Pavesi (1), who isolated the alkaloid by extracting the unripe seed-capsules of *Papaver dubium* with petroleum ether. The name was derived from *απορεω* (=dubito). Aporeine has not been found in extracts from *Papaver somniferum*.

The base crystallizes from petroleum ether in greenish yellow prisms, which melt at 88° to 89° to a fluorescent liquid (decomp. 225°). It may be distilled in an inert atmosphere. It is readily soluble in benzene, xylene, carbon disulphide, chloroform, bromoform, acetone, ethyl acetate, etc., sparingly soluble in petroleum ether of b. p. 45° to 50° (hot, 11%, cold, 3.5%). The solutions are fluorescent, especially in magnesium light. Aporeine reacts faintly basic in alcohol solution and forms well-crystallized salts, which however, are acid in reaction. It is optically active, $[\alpha]_D^{15} = +75.19°$. Aporeine in dilute sulphuric acid reduces potassium permanganate rapidly (2). The salts of aporeine are precipitated by most of the alkaloid reagents. With nitric-sulphuric acid mixture, a violet color is observed; Fröhde's reagent gives a gray blue, turning green and then yellow; Marquis' reagent gives a green color, turning through blue to black.

Aporeine produces on the tongue a burning feeling, then dulls the sense. In frogs it has a tetanic action similar to thebaine (1) (4).

The hydrochloride of aporeine, on exposure to sunlight for 14 days, yielded a new base, aporegenine, which crystallized in white needles, but could not be obtained pure.

A second alkaloid, aporeidine, which crystallizes from alcohol in rhombic plates of melting point 176° to 178° was obtained from the latex of *Papaver dubium* along with aporeine, but is apparently formed from the latter by the action of light and air (2) (3).

APOREINE HYDROCHLORIDE crystallizes from water or alcohol in shining plates which begin to decomp. at 215°, and melt at 230°; the salt sublimes at 220° to 240° in a carbon dioxide atmosphere. With chloroplatinic acid it yields the PLATINICHLORIDE $(C_{18}H_{16}O_2N \cdot HCl)_2PtCl_4$, as rhombic plates (2). APOREINE HYDROBROMIDE, yellow scales, becoming colored at 190°, and melting above 210° (decomp.) (3). APOREINE HYDRIODIDE, yellow-green scales from water, darkening at 200° to 210°, melting at 250° to 255° (3). APOREINE SULPHATE, felted crystals which decompose when heated (3). APOREINE NITRATE decomp. 200° to 240° (3). APOREINE BINOXALATE, plates from alcohol, m. p. 89° to 90° (3). APOREINE BIMALATE, m. p. 198° (decomp.) (3). APOREINE BITARTRATE, needles which decomp. at 190° (3). APOREINE CITRATE $C_{18}H_{16}O_2N \cdot C_6H_8O_7$, needles of m. p. 81° to 82° (3). The ACETATE, BENZOATE, and SALICYLATE are not crystalline (3).

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Part II. THE PHENANTHRENE ALKALOIDS

MORPHINE

In 1803 Derosne (1), by extraction of opium with water and precipitation of the extract with potassium carbonate, obtained a crystalline substance which he named "salt of opium." He observed its solubility in acids and precipitation by bases, but failed to recognize its basic character. Sertürner (2) believed that Derosne's salt of opium was morphine acid meconate; Pelletier (3) and Robiquet (4) (5) considered it to have been narcotine.

In a little-noticed paper (6) (7) (8) the pharmacist Sertürner, of Einbeck in Hannover, described the isolation of the pure base in 1805. In later papers (2) (9) (10) (11) (1817) he again called attention to his discovery of a vegetable base which was capable of neutralizing acids and forming salts.* The publications aroused immediate interest, and Sertürner's results were verified by Robiquet (12) (13) within the same year.[76] Further researches by Robiquet (15) (16), Pelletier (3) (17), Couerbe (18), Dublanc (19) (20), Duflos (21), and Robinet (22) resulted in improvement in the methods of separation, as well as the isolation, of new substances (narcotine, narceine, meconin, etc.).*

Pelletier (3) investigated the colored material formed in the reaction between ferric chloride and morphine. He isolated a colored crystalline substance which he called iron morphite. He also studied the action of iodine and chlorine on morphine (23). Determinations of the hydrate water and acid equivalent of morphine were carried out by Robiquet (15) (16). Choulant (24) (25) prepared and analyzed a number of salts; Serullas (26) investigated the action of iodic acid, and determined its sensitivity as a reagent for morphine. Robinet (22) noted the solubility of morphine in lime water, but did not realize its phenolic nature.

The first elementary analyses by Liebig (27) (1831) gave morphine the formula $C_{34}H_{36}O_6N_2$. Regnault (28) (29) found values for $C_{35}H_{40}O_6N_2$. (*Cf.* Dumas (35), Pelletier (36).) In 1847 Laurent (30) published the formula $C_{34}H_{38}O_6N_2$, corresponding to the now accepted formula $C_{17}H_{19}O_3N$. Raoult (31) found a molecular weight in acetic acid corresponding to $(C_{17}H_{19}O_3N)_2$. Later determinations by Eykman (32) and Von Klobukow (33) showed the simple formula to be the correct one. (See also Bertrand and Meyer (34).)

Morphine is obtained from opium, the dried juices which exude from the scratched unripe seed-capsules of the opium poppy, *Papaver somniferum*. The amount of morphine present in opium varies between wide limits; in a good grade of opium it averages 10%, al-

* See Appendix, p. 359.

[76] Pelletier (3) points out that his compatriot Séguin, in a report before the Academy of Sciences in 1804 described the isolation and properties of morphine and even suggested its basic nature. This paper was first published in 1814 (14).

though samples containing over 20% have been reported. (For a full discussion see Jermstad (37).) Poppy seeds are alkaloid-free; morphine is first detectable in the plant 36 days after sprouting of the seeds (38).*

Charbonnier (39) found morphine in *Argemone mexicana* (*Papaver spinosum*) (*cf.* Dragendorff (40)), and Baudet and Adrian (41) reported it in *Escholtzia californica*. It is said by Ladenburg (42) to occur also in American hops (*Humulus lupulus* L., Cannabinaceæ).[77] *Papaver rhœas* is said to contain morphine (44); Hesse (45) (46) (47) found only rhœadine.*

Morphine crystallizes from dilute alcohol in small rhombic prisms (48), often having the appearance of needles (49); crystal measurements have been published by Brooke (50), Schabus (51), Rammelsberg (52), Lang (53), Decharme (54), and Wherry (55). The hydrated crystals have the specific gravity 1.317 to 1.326 (56), (1.32 (55)). The refractive indices were found by Kley (57) (58) to be 1.63 and 1.62; Keenan (59) gives $n_D = 1.580$; Wright (60) and Wherry and Yanovski (55) find n_D: $\alpha = 1.580$, $\beta = 1.625$, $\gamma = 1.650$ (1.645). The base usually crystallizes with one molecule of hydrate water, which is lost at about 100° (61) (62). The anhydrous substance melts at 247° to 248° (253° to 254° corr.) (63) with decomposition.

Morphine sublimes crystalline at temperatures between 150° and 200° (64) (65). Vacuum micro-sublimation methods for identification of the alkaloid are described by Tunmann (66) and Heiduschka and Meisner (67). Krafft and Weilandt (68) observed smooth sublimation in high vacuum at 191° to 193°. (*Cf.* Kempf (63).) Morphine has been shown present in the smoke from the opium pipe (69).

Methyl alcohol (55) (70) or amyl alcohol (71) are recommended for recrystallization; from anisole the base crystallizes in anhydrous prisms (72). It is very slightly soluble in alkali carbonates, readily soluble in alkali hydroxides (73), sparingly in alkaline-earth hydroxides (74). Ammonia precipitates the base crystalline from solutions of its salts with acids; it is somewhat more soluble in ammonia than in water. The solubilities of morphine in various media are tabulated below. It should be noted that the state of aggregation influences the solubility of the alkaloid markedly; amorphous or freshly precipitated it is said to be many times more soluble than when crystalline (75).

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* See Appendix, p. 359.

[77] Williamson (43) in a series of papers on Hopeine, from *Humulus lupulus*, claims that this base, while closely resembling morphine, differs from it in many respects. Along with Hopeine he found another alkaloid which he called isomorphine, whose identity with morphine was not excluded.

*Table of solubilities**

[Grams of morphine base in 100 g. solvent]

Solvent	Solubility	Observer
Water	0.01 (10°), 0.04 (40°), 0.08 (60°), 0.125 (80°), 0.165 (90°), 0.217 (100°).	Chastaing (74).
Do	0.1 (cold), 0.25 (boiling)	Duflos (21).
Do	0.028	Müller (76).
Do	0.019 (20°)	Guild (77).
Water saturated with ether	0.044	Müller (76).
Ether saturated with water	0.009	Do. (76).
Ether	0.016 (boiling)	Prescott (75).
Do	0.013	Müller (76).
Ether (absol.)	0.023 (10°)	Florio (78).
Alcohol 75%	0.223 (10.8°), 1.95 (78°)	Do. (78).
Alcohol 90%	0.377 (10.6°), 2.991 (78°)	Do. (78).
Alcohol (absol.)	1.132 (10.6°), 8.623 (78°)	Do. (78).
Methyl alcohol	1.675 (10.8°), 8.466 (56°)	Do. (78).
Amyl alcohol	0.26 (cold), 1.1 (boiling)	Kubly (79), Prescott (75).
Benzyl alcohol	50 (boiling), 21.5 (20°)	Fabre (80).
Ethyl acetate	0.213	Kubly (79).
Do	0.18	Müller (76).
Chloroform	0.1 (cold)	Burg (81).
Do	0.023 (boiling)	Prescott (75).
Do	0.040 (9.4°), 1.235 (56°)	Florio (78).
Do	0.065	Müller (76).
Chloroform+10% alcohol	0.9 (cold)	Burg (81).
Carbon tetrachloride	0.032 (17°)	Schindelmeiser (82).
Do	0.015	Müller (76).
Benzene	0.020 (9.4°)	Florio (78).
Do	0.011 (boiling)	Prescott (75).
Do	0.062	Müller (76).
Anisole	0.00 (9°), 0.95 (100°), 4.90 (150°)	Fouquet (72).
Nitrobenzene	0.51 (20°), 10.5 (boiling)	Fabre (80).
Petroleum ether	0.086	Müller (76).
Olive oil	0.00	Pettenkofer (83).
Ammonia 0.1 *N*	0.095 (25°)	Heiduschka (84).
Ammonia 0.2 *N*	0.123 (25°)	Do. (84).
Ammonia *N*	0.32 (25°)	Do. (84).
Ammonia, sp. gr. 0.97	0.85	Duflos (21).

*See Appendix, p. 359.

Morphine is levorotatory, $[\alpha]_D^{23} = -130.9°$, in methyl alcoholic solution (C = 2.292) (70); $[\alpha]_D = -131.7°$ (methyl alcohol, p = 1) (55); in aqueous solution as the sodium salt, $[\alpha]_D^{22.5} = -70.23°$ (p = 2) (85) (*cf.* Bouchardat (86)). For morphine hydrochloride (hydrated) Hesse (85) found $[\alpha]_D^{15} = -99.54°$ (p = 1), and for the hydrated sulphate, the same value. The rotatory power decreases with increasing concentration of the solution. Tykociner (87) reported values for a large number of salts, all in the neighborhood of $[\alpha]_D = -128°$; for the base he gave $[\alpha]_D = -140.5°$ (absolute alcohol, p = 0.25 to 0.45).

The absorption spectrum has been studied by Hartley (88) and Kitasato (89), that in the ultra-violet by Brustier (90), and Steiner (91). Gompel and Henri (92) compared the ultra-violet absorption spectra of morphine, codeine, and apomorphine with that of phenanthrene. Meyer (93) examined the absorption by the colored solution of morphine in Erdmann's reagent (sulphuric-nitric acid).

The heat of combustion of morphine hydrate is 2145.2 Cal. at constant volume, 2146.7 Cal. at constant pressure; the heat of hydration is 3.6 Cal. The heats of reaction of the base with a number of acids and with alkali have also been determined (94) (95).

Morphine is a monoacid base, whose salts react neutral to litmus or methyl orange. The free base turns litmus blue (95), and red

helianthin to yellow; in aqueous solution it does not affect phenolphthalein, but when water is added to an alcoholic solution of morphine containing phenolphthalein, a rose color appears. The phenolic hydroxyl of morphine is sufficiently acidic to turn Poirrier's Blue (C4B) reddened by alkali to violet (94). The pH value for morphine salts averages 4.68; methyl red should be used for titrations involving morphine (96) (97) (98). The isoelectric point for morphine lies at pH 8.96 (Kolthoff (99) (100)), but the base shows its minimum solubility in the range pH 8.4–9.4 (101). For titration methods and use of indicators see further refs. 102–113 (not a complete bibliography of the subject).

A large number of color and precipitation tests for morphine have been described; in the table below are given the most important, and those having especial historic interest:*

Color and precipitation reactions

Reagent	Reaction	Observer
Robiquet's test, Ferric chloride	Deep blue, disappearing on warming or with excess of acid.	Pelletier (17).
Nitric acid, (sp. gr. 1.42)	With solid base or salts, intense orange-red color, destroyed by sodium thiosulphate.	Duflos (21).
Iodic acid	Iodine liberated; sensitivity increased by addition of ammonia (114); *cf.* Fulton (115).	Serullas (26).
Ferric chloride and pot. ferricyanide.	Berlin-blue; sensitive 1:100,000. *Cf.* Hesse (62), Armitage (116).	Schaer (117).
Sugar and conc. H_2SO_4	Base mixed with 6 parts of sugar, a drop of conc. H_2SO_4 added; purple-red turning blue-green then yellow; sensitive to 0.01 mg. A drop of bromine water increases sensitivity (118).	Schneider (119).
40% formaldehyde (2 drops) in conc. H_2SO_4 (3 c. c.).	Violet-red, becoming blue; *cf.* Kobert (120), Elias (121). Modified by addition of conc. HNO_3, Fulton (115).	Marquis (122).
Sodium nitrite	In acid solution, yellow, becoming orange with alkali. *Cf.* Riegel and Williams (123).	Wieland and Kappelmeier (124).
Diazotized sulphanilic acid	2% solution of the reagent is added to a solution of morphine salt, and made alkaline with sodium carbonate; red color. Action of other diazonium salts is also described.	Lautenschläger (125).
Nitric acid or sodium hypochlorite	Reagent added to a warm solution of the base in conc. sulphuric acid; carmine.	Erdmann (126), Husemann (127). *Cf.* Couerbe (128).
Perchloric acid	On heating, violet, becoming brown	Fraude (129).
Potassium perchlorate free from chlorate.	Reagent added to base in conc. H_2SO_4; brown. *Cf.* Rosenthaler (130).	Grove (131), Siebold (132).
Iodine in potassium iodide solution (Wagner's reagent).	Brown cryst. precip.	Jörgensen (133), Wagner (134).
Bromine water	Boil solution of morphine salt with an excess of reagent, neutralize with $CaCO_3$, and boil; bright red, sensitive 1:1,200.	Eiloart (135).
Chlorine water	Green-yellow color; addition of NH_4OH turns it brown-yellow. Not given by codeine.	Marmé (136), Flückiger (137).
Iodine chloride	Iodine separates in the cold.	Dittmar (138).
Conc. HCl-conc. H_2SO_4 mixture	Heated to 100° to 120°, purple	Pellagri (139), *cf.* Fulton (115).
Molybdic acid in conc. H_2SO_4	Violet turning blue then dirty green, finally colorless.	Fröhde (140).
Ammon. molybdate (0.1 g.) in conc. H_2SO_4 (1 c. c.) (Fröhde-Buckingham).	Cold, lilac; on heating, green. With KNO_3 becomes red, then yellow.	Bruylants (141).
Sat. sol. titanic oxide in conc. H_2SO_4.	Shaken with a solution of base in conc. H_2SO_4, blood-red; color fades with water.	Reichard (142).
Trisodium phosphate in conc. H_2SO_4.	On warming, violet, turning red with water, from which chloroform extracts a blue color.	Vulpius (143). *Cf.* Ekkert (144).
Potassium arsenate in conc. H_2SO_4.	On heating, blue-violet, turning brown; diluted, green, chloroform extracts a violet color. *Cf.* Reichard (145).	Donath (146), Tattersall (147).
Potassium chlorate in conc. H_2SO_4.	Grass green, rose color at edges	Donath (146).
Ammonium sulphouranate in conc. H_2SO_4.	Dirty green color on warming	Bronciner (148).

* See Appendix, p. 360

Color and precipitation reactions—Continued

Reagent	Reaction	Observer
Vanillin or piperonal	Evap. an alcoholic sol. of base and reagent with a few drops of 0.5 *N* H_2SO_4 on steam; red-violet color.	Van Itallie and Steenhauer (149).
Uranyl acetate or ferric acetate with formaldehyde.	Reagent added to base in conc. H_2SO_4. *Cf.* Aloy (150) (151).	Aloy (152).
Benzidine	0.01 g. base added to a few c. c. conc. H_2SO_4 containing 0.01 g. reagent; yellow, becoming brown, then dark green; add to water, violet, extracted by chloroform. Test given also by codeine, dionin, heroin, apomorphine.	Ekkert (153).
Hydroferrocyanic acid, hydroferricyanic acid.	Microchemical examination of precipitate. *Cf.* Plugge (154).	Cumming and Brown (155).
Silicoduodecitungstic acid	Buff-colored precip.; mod. sol. in alcohol or dil. acids. Sensitive 1:16,000.	North and Beal (156), Heiduschka and Wolf (157), Bertrand (158).
Potassium chromate, potassium dichromate.	Precip. of chromate and free base. Brown precip., composition uncertain.	Plugge (159).
Reinecke's salt	Characteristic crystals on microscope slide	Rosenthaler (160).
Sodium vanadate and copper sulphate in dil. acetic acid.	Precip. in solutions stronger than 0.1%	Jaworoski (161).
0.1% solution of sodium tungstate	Shake with alkaloid dissolved in a few c. c. conc. H_2SO_4; impermanent blue-violet.	Reichard (142).
0.1% solution of ammonium metavanadate, H_2SO_4 added until yellow color disappears.	Add morphine salt to reagent and warm; permanent bright green; very dilute, blue-green.	Do. (142).
Ferrous sulphate, ammonia	Base warmed with conc. H_2SO_4, a crystal of $FeSO_4$ added, poured into conc. ammonia; red-violet between layers; on shaking, blue. Not given by codeine.	Jorissen (162).
3% hydrogen peroxide	Reagent layered onto a solution of base in 2 c. c. conc. H_2SO_4; yellow-brown to emerald ring; on rotating, yellow layer over emerald.	Ekkert (163).
Lead peroxide	Base in 5% sulphuric acid shaken with PbO_2; pink solution, brown with ammonia.	Fleury (164).
Silver nitrate	Silver precip. in 30 to 60 min	Hager (165).
Formaldehyde-stannous chloride	Base in excess formaldehyde, with a drop of $SnCl_2$ sol., evap. dry; permanent blue-violet.	Reichard (166).
Ammoniacal copper sulphate	Blue solution becomes green on boiling	Duflos (21), Nadler (167), Lindo (168).
H_2O_2, ammonia, and copper	The liquids are added to morphine salt, stirred with copper wire; deep port-wine color, gas-evolution, sensitive 0.02 mg. Apomorphine gives orange color; other common alkaloids, no color.	Oliver (169).
Magnol (basic magnesium hypochlorite) in acetic acid.	Base dissolved in reagent, layered onto conc. H_2SO_4; yellow-brown ring; in 3 hours color of Hessian Purple-B; in 24 hours, yellow layer over Rhodulin Red-G layer, over pale dark blue layer.	David (170).

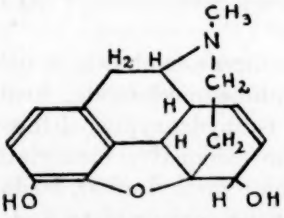
A sensitive biological test is described by Hermann (171), wherein as little as 0.01 mg. of morphine injected subcutaneously on the back of a white mouse causes the mouse to lay its tail up over the back. (Straub test.)

Quantitative determinations of morphine in opium, as well as for forensic purposes have been described in great number. These depend mostly upon isolation of the morphine itself (Dieterich (172), Pape (173)), upon its precipitation quantitatively by some reagent as Mayer's (see Heikel (174), Ionesco-Matiu (175)), or Wagner's (Prescott and Gordin (176)), and upon its reducing action, as in Kieffer's (177) ferricyanide method, or in the iodic acid method. Colorimetric determinations using iodic acid or Marquis' reagent are described by Heiduschka (178), Miller (179), Stein (180), and Van Itallie (181). For a critical discussion of methods of estimation see Taylor (182) or Schmidt (183).

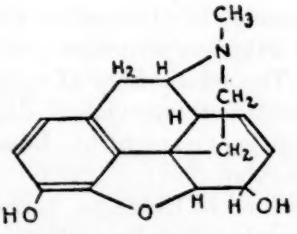
The course of exhaustive methylation shows that the nitrogen atom in morphine is tertiary, and forms part of a ring. It carries a methyl group (184), which may be split off by the action of cyanogen bromide or chloride, yielding through the cyano derivative, normorphine (185) (186) (187), in which the N-methyl group has been replaced by hydrogen. Certain morphine derivatives, as codeine and diacetylmorphine, are similarly N-demethylated by nitrous acid, although morphine itself is oxidized by this reagent to pseudomorphine (188).

One of the three oxygen atoms is present in a phenolic hydroxyl, which is responsible for the intense color reaction of morphine with ferric chloride and for its solubility in alkali; the base is precipitated from its alkali salts by carbon dioxide or ammonium chloride. Phenol ethers result when morphine is treated with alkyl halide and alkali, or with diazomethane. The second oxygen forms an alcoholic hydroxyl group; this etherifies only with difficulty, but is acetylated readily. With phosphorous halides it is substituted by halogen. (See halogenomorphides, p. 209.) The third oxygen is indifferent, and is bound in an ether linkage; during the reduction of numerous morphine derivatives, reductive scission of the cyclic ether group takes place, and the oxygen then appears in the form of a new phenolic hydroxyl group.

The reactive groups of morphine are arranged on a partially hydrogenated phenanthrene skeleton. The exact location and nature of the linkage of these groups has been the subject of intensive research for over half a century. The two most probable structural formulas developed in this time are represented below:



Knorr-Horlein (1907), as modified by Wieland and Kotake, 1925



Gulland and Robinson (1925)

Since evidence for these formulas has been largely gathered from the chemistry of codeine (morphine methyl ether), and of thebaine, it will be developed in a separate section (p. 336). In the following paragraphs the more important reactions of morphine itself will be considered.*

Morphine is marked by the ease with which it is oxidized. It reduces gold (38) and silver (38) (165) salts in the cold; the decomposition of the platinichloride in hot water is probably due to oxidation

* See Appendix, p. 366.

(189) (190). Many of the tests tabulated above depend upon this ease of oxidation, as those with ammoniacal copper solution, iodic acid, potassium ferricyanide, etc. It is oxidized readily by permanganate (191) and, in alkaline solution, by air. The product of morphine oxidation is usually the dimolecular substance, pseudomorphine (p. 170); according to Lamal (192) solutions of morphine salts (especially the acetate) deposit crystals of pseudomorphine after long standing.*

Morphine is also oxidized to pseudomorphine during electrolysis (193) or by certain enzymes (e. g., from *Russula delica* (194) (195)).

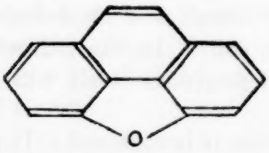
By nitric acid oxidation of morphine Chastaing (74) obtained a tetrabasic acid, which was converted to picric acid by further action of nitric acid.*

Like many other tertiary ring-nitrogen compounds, morphine forms an amine oxide with hydrogen peroxide (196). Ozone acts to open the aromatic ring, with loss of two carbon atoms; the same product, codinal, is obtained from ozonization of codeine (197) (p. 182), a result which is only explicable by the assumption that the carbon atom carrying the phenolic hydroxyl group in morphine and that carrying the methoxyl in codeine were removed in the ozonolysis.

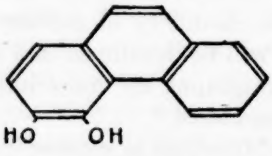
Morphine-blue is a crystalline, highly colored substance having the composition $C_{26}H_{22}O_4N_2$, which is formed by air-oxidation of the phenolic products obtained by heating morphine with sulphuric acid in the presence of oxalic, malonic, or succinic acids (198).

When morphine is heated with potassium hydroxide, methylamine is evolved (191) (199); with alcoholic potash at 180 °, ethylmethylamine is split out (200). Barth and Weidel (191) isolated protocatechuic acid from the melt of morphine with potassium hydroxide. By dry distillation over zinc-dust, phenanthrene is formed in about 20% yield; the other products isolated are ammonia, trimethylamine, a homolog of thebenidine (p. 325), and a base, morphidine, $C_{17}H_{17}N$, of unknown structure (201) (202) (203).

The relationship of morphine to phenanthrene is shown in other somewhat less violent degradations; morphine methiodide, heated with acetic anhydride, breaks down into 3, 4-dihydroxyphenanthrene, morphol (204) (p. 281). In particular, the exhaustive methylation method of Hofmann, carried out on morphine methyl ether, leads to morphenol or its methyl ether, which may be converted to 3, 4, 5-trihydroxyphenanthrene by the action of molten alkali (205.) (See p. 283).



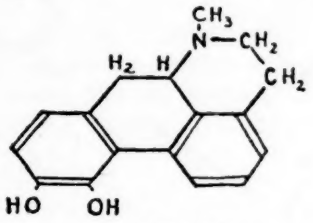
Morphenol



Morphol

* See Appendix, p. 360.

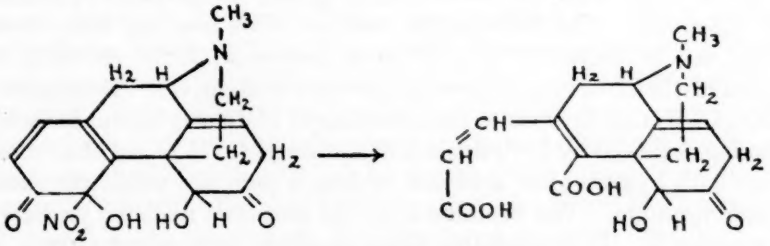
With strong acids, morphine undergoes a deep-seated rearrangement into apomorphine, an isoquinoline derivative. The structure of this substance and the mechanism of its formation are discussed in a separate section (p. 261).



Apomorphine

Fulton (115) reports the formation of a crystalline substance resembling apomorphine when morphine is heated with concentrated sulphuric acid at 40°.

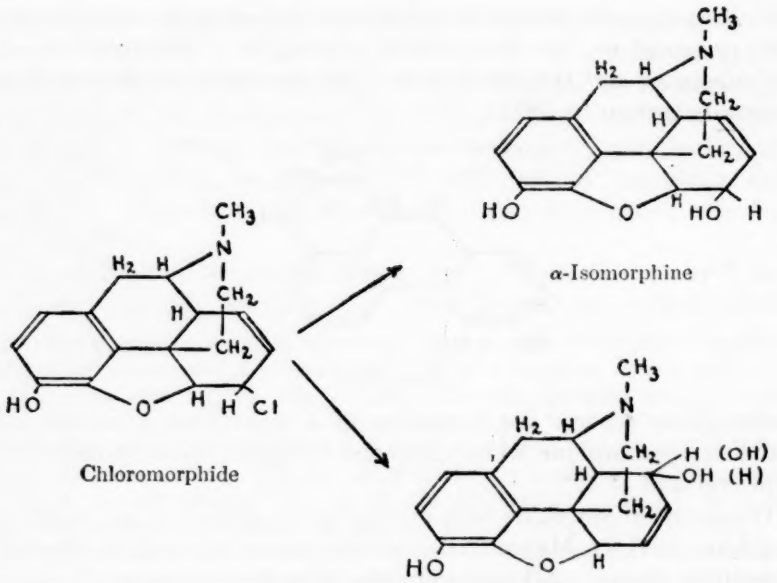
Treatment of morphine with nitrous gases converts it to 2-nitrosomorphine (124) (*cf.* Mayer (206)), which may be reduced to the corresponding amine. 2-Aminomorphine behaves as an aromatic amine, and diazotizes readily. With 2-nitrosomorphine is formed also a quinitrol-base, apparently carrying a nitro group in the 4-position; when warmed, it suffers internal oxidation, yielding the dibasic morphinic acid (124):



The dihydromorphinic acid prepared by Speyer and Popp (207) by saponification of the ozonization product from dihydrocodeine (see p. 187) is thought to be closely related to Wieland's morphinic acid.

Benzene diazonium chloride couples with morphine to form 2-phenylazomorphine (124). This substance rearranges under the influence of concentrated sulphuric acid to 2-phenylazoapomorphine (208).

By the action of phosphorous halides (70) (209) or thionyl chloride (124) the alcoholic hydroxyl group of morphine is replaced by halogen. Chloromorphide exists in two forms, believed to be stereoisomers; only one bromomorphide is known. The halogenomorphides hydrolyze with dilute acids on heating, whereby halogen is replaced by hydroxyl, and three isomers of morphine are formed (70) (210). The constitution of the morphine isomers is considered on page 219.



Bromine reacts with morphine to form α- or β-tetrabromomorphine, $C_{17}H_{15}O_3NBr_4$. Sodium ethylate or silver oxide removes part of the bromine from the α-compound, giving a crystalline quinone-like substance. The β-derivative loses all of its bromine with silver oxide, and is converted to amorphous products (211). Nothing is known of the structure of these tetrabromo derivatives. Bromomorphine, $C_{17}H_{18}O_3NBr$, results from treatment of diacetylmorphine with bromine, followed by hydrolysis (212). Morel (213) found that morphine with hydrobromic acid and hydrogen peroxide yields the same bromomorphine. The bromine is in the aromatic nucleus, probably in position 2. It precipitates silver bromide with silver nitrate in dilute nitric acid, apparently forming nitrosomorphine or nitromorphine (212).

Morphine gives a brown crystalline precipitate of superiodide with iodine in potassium iodide; reducing agents regenerate morphine from the superiodide (133) (214).

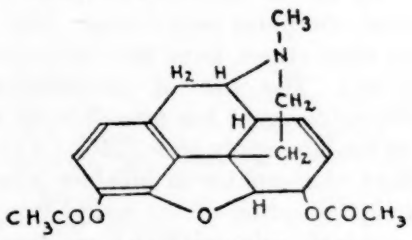
Hydrogen sulphide acts upon morphine in the presence of oxygen; the products have not been studied (215).

Morphine is recovered unchanged from treatment with Grignard's reagent (216).

The so-called polymers of morphine (dimorphine, trimorphine, and tetramorphine), which formed the subject of a long series of papers by Beckett and Wright (217) (218) (219) (220), were apparently complex noncrystalline mixtures.

Both the alcoholic and phenolic hydroxyl of morphine may be esterified. When morphine is heated with acetic acid two mono-

acetyl derivatives are formed; α-acetylmorphine and β-acetylmorphine probably have respectively the phenolic and alcoholic hydroxyl groups acetylated (217) (221). Danckwortt (222) failed to find any trace of the γ-acetylmorphine reported by Beckett and Wright (217). A diacetyl derivative results from the action of acetic anhydride (195) (217); it is more easily prepared using acetyl chloride (223). Diacetylmorphine comes on the market as a narcotic in the form of its salts under the names Heroin, Diamorphine, or Acetomorphine. It hydrolyzes with boiling water to α-acetylmorphine, and finally to morphine acetate (221).*



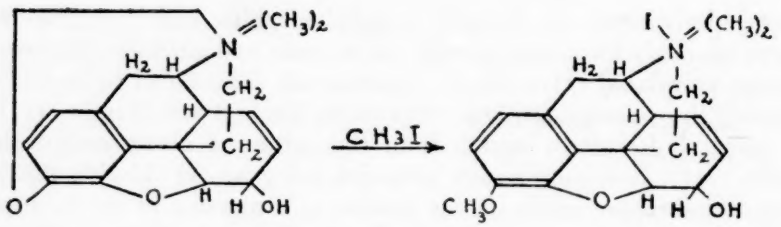
Diacetylmorphine (Heroin)

A triacetylmorphine was reported by Causse (224) (225) (226) (227), who sought to prove the presence of a carbonyl group in morphine; the base was treated with acetic anhydride, sodium acetate, and zinc dust, whereby the carbonyl group was assumed to be reduced to an alcoholic hydroxyl, which then acetylated. Under Causse's conditions Knorr (228) obtained only diacetylmorphine. Diacetylmorphine is unaffected by further treatment with acetic anhydride at 180° (229). The triacetylmorphine of Knoll & Co. (230), which is formed through the action of acetic anhydride-sulphuric acid mixture at 85°, evidently has an acetyl group substituted into the nucleus (compare the analogous reaction of codeine and narcotine). Polstorff (231) believed to have prepared tribenzoylmorphine; this was shown by Wright (232) to be dibenzoylmorphine. Benzoylacetylmorphines are also known (233), as well as other mixed esters. (See descriptive section.) Knoll & Co. (230) describe a dibenzoylacetylmorphine.

Morphine adds alkyl halides readily; the methiodide, when treated with alkali, yields morphine methohydroxide, which was shown by Vongerichten (212) (234) to have a phenolbetaine type of structure. Like many other compounds of this structure (*cf.* protopapaverine, p. 16, N-methylnorpapaverinium betaine, p. 11), the betaine adds methyl iodide, giving in this case codeine methiodide.

The alkylation of morphine on the phenolic hydroxyl has been very extensively investigated, because of its importance as a means of converting morphine to its methyl ether, codeine. A wide variety

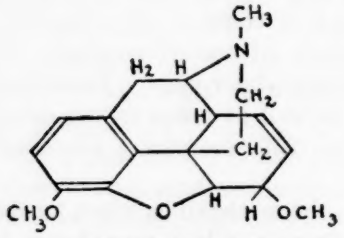
* See Appendix, p. 361.



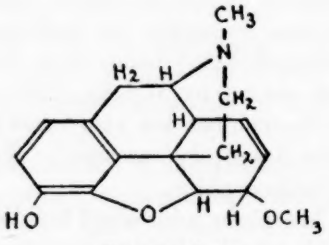
of agents has been employed for this, as diazomethane (235) (236) dimethyl sulphate and alkali (237), or trimethylphenylammonium hydroxide (238).[78] By similar methods, morphine ethyl ether (223) (codethylin or dionin), morphine benzyl ether (223) (239) (peronin) as well as numerous other ethers, have been prepared. (See descriptive section, p. 156.) The use of trimethylphenylammonium hydroxide as an alkylating agent has proved to be particularly convenient for work on the laboratory scale (240) (241).

Through treatment of morphine in alkaline solution with acetobromoglucose and saponification of the acetyl compound, Mannich (242) was able to prepare a glucoside of morphine; this hydrolyzed with acid into morphine and glucose.

Both hydroxyl groups of morphine can be methylated, using dimethyl sulphate and alkali (243) (244). To avoid the formation of quaternary alkylates, Mannich (245) methylated morphine-N-oxide, and by reduction of the N-oxide product with sulphur dioxide obtained the base, morphine dimethyl ether (codeine methyl ether). If the phenolic hydroxyl of morphine is protected during alkylation with some group which can later be removed (as $-CH_2OCH_3$), an ether in which the alcoholic hydroxyl group is methylated (heterocodeine) (245) can be prepared.



Dimethylmorphine



Heterocodeine

Codeine has not been converted back to morphine.

Hydrogenation of morphine was first carried out by Oldenberg (246) (247) and Skita (248) with hydrogen in the presence of palladium. A nickel suboxide catalyst has also been used (249). By hydrogenation of crude opium extract, dihydromorphine may be isolated as such directly (250).

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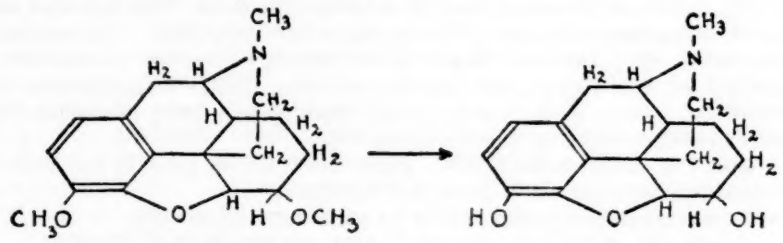
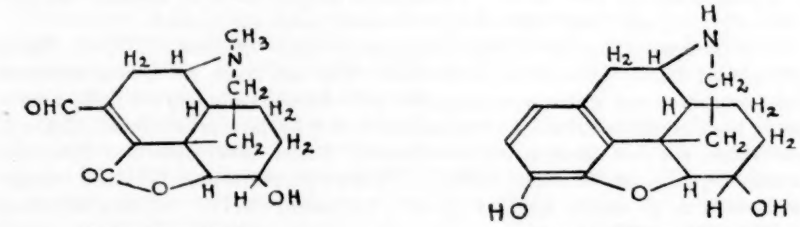
[78] A complete list of methods is given under codeine, p. 175.

Dihydromorphine ("Hydromorphine") behaves toward ferric chloride, silver nitrate, and the reagents of Husemann, Marquis, and Fröhde very much like morphine itself. It yields on methylation dihydrocodeine, identical with the dihydrocodeine obtained from hydrogenation of codeine (251) (252). Due to the great stability of these hydrogenated alkaloids, dihydrocodeine can be converted back to dihydromorphine by boiling with hydriodic acid (253). Dihydromorphine dimethyl ether (245) is identical with tetrahydrothebaine (254), which demethylates with hydriodic acid or aluminum chloride to give dihydromorphine (255).*



Tetrahydrothebaine Dihydromorphine

Ozonization of dihydromorphine results in rupture of the aromatic ring, with formation of dihydrocodinal (256).



Dihydrocodinal Dihydronormorphine

The action of cyanogen bromide on dihydromorphine has been investigated by Von Braun (185). Hydrolysis of the cyano compound first formed gave dihydronormorphine, which was also obtained from hydrogenation of normorphine (257).

Dihydromorphine-N-oxide and the sulphonic acids from dihydromorphine were studied by Speyer and Becker (258).

Another reduction product of morphine, desoxymorphine, $C_{17}H_{19}O_2N$, was prepared by Lees (70) through reduction of chloromorphide with tin and hydrochloric acid. Nothing is known of its structure. The dihydrodesoxymorphine which was claimed (259) to be formed as a by-product when chlorodihydrocodide is treated with sodium methylate is probably a desoxymorphine; the supposed dihydrodesoxycodeine from which it can be obtained by demethylation is actually a nonphenolic desoxycodeine. A dihydrodesoxymorphine results from catalytic hydrogenation of α-chloromorphide with palladium; it methylates to yield dihydrodesoxycodeine-D. (See p. 239 (386).) Tetrahydrodesoxymorphine has been prepared by demethylation of tetrahydrodesoxycodeine (393).

Morphine does not reduce with sodium in alcohol, nor with zinc and acetic acid (260).

* See Appendix, p. 361.

Hydrogenation of morphine in warm strongly acid solution in the presence of a large excess of palladium or platinum catalyst leads to the formation of a hydrogenated keto derivative, dihydromorphinone, which has come on the market under the trade name Dilaudid (261) (262).

Descriptive Part (Morphine)

I. SALTS *

MORPHINE: B=$C_{17}H_{19}O_3N$. —HYDROCHLORIDE, B·HCl·$3H_2O$, silky needles from water (29); cryst. anhydrous from alcohol; m. p. 200°. $[\alpha]_D^{25}=-111.5°$ (C=2.240) (70), *cf.* Hesse (85) (263). Sol. in 17.5 parts water 25°, 0.5 parts at 100°; 41.5 parts alcohol 25°, 37 parts at 60°; (anhydrous) in 51 parts methanol at 15°; sol. in 19 parts glycerine, insol. in ether or chloroform. The hydrated salt loses its crystal-water in vacuum or on drying at 100° (264) (265). Thermochemistry, Leroy (94); –Mercurichloride, B·HCl·$2HgCl_2$, crystalline precip. (267); sparingly sol. cold water or alcohol, very sol. conc. HCl; –Platinichloride, $(B·HCl)_2PtCl_4$, yellow curdy precip., cryst. from water (268); –Stibnichloride, $(B·HCl)_2·SbCl_5+4H_2O$, light brown plates (269).

—ZINC CHLORIDE: B·$ZnCl_2·2H_2O$, glassy cryst., sol. in water or hot alcohol. From HCl solution, cryst. of B·$ZnCl_2·7H_2O$ (266).

—NITRATE, grouped needles, sol. in 1.5 parts water (2) (9) (25).

—PHOSPHATE, cryst. cubes, diff. sol; –Acid salt, clumps of needles (270).

—CARBONATE, from solution of morphine in water under CO_2 pressure; short prisms, sol. in 4 parts water, decomp. on warming (24).

—HYDROBROMIDE: B·HBr·$2H_2O$, tufts of long white needles from water; loses its crystal-water at 100° (271). Crystallizes anhydrous from alcohol. $[\alpha]_D^{15}=-100.4°$ (C=2.49) (70). Soluble in hot water, sparingly in cold.

—HYDRIODIDE (23): B·HI·$2H_2O$, rosettes of silky needles, (271), *cf.* Bauer (272), B·HI·$3H_2O$, Kunz (273), B·HI·H_2O. The salt loses its crystal-water at 100°; soluble in hot water, sparingly in cold; –Mercuriodide, B·HI·HgI_2, microscopic needles (274) (275). —TETRAIODIDE, B·HI_4, dark brown cryst., diff. sol. cold water, sol. hot alcohol, hot ether (133). Bauer (272) described B_2I_3, red-brown crystals, *cf.* Winkler (276). —TETRACHLORIODIDE, B·$HICl_4$, orange needles from gl. acetic acid, m. p. 78° (decomp.) (277). —BISMUTHIODIDE, $(B·HI)_3·(BiI_3)_4$ (278).

—HYDROFLUORIDE (279): colorless prisms, sl. sol. water, insol. alcohol, ether. —BOROFLUORIDE, B·HBF_4, fine needles (280). —PHOSPHOFLUORIDE, B·HPF_6, needles, easily sol. in water (281).

—SULPHATE: $B_2H_2SO_4+5H_2O$, white needles (radiating tufts of flat-ended prisms, illustration (49)) sol. in 23 parts cold water, 15.5 parts at 25°, 0.7 parts at 80°; soluble in 452 parts alcohol at 25°, 192 parts at 60°; insol. in chloroform, ether (29) (36) (282). At 110° it loses $3H_2O$, the remaining $2H_2O$ at 130° with partial decomp. Thermochemistry, Leroy (94). $n_D=1.545$ (59).

—THIOSULPHATE: $B_2H_2S_2O_3+4H_2O$, silky needles sol. in 32 parts cold water, 1,050 parts cold alcohol (283). —DITHIONATE, $B_2·H_2S_2O_6+2H_2O$, needles, very sol. in water. It loses SO_2 at 170°, leaving Morphine sulphate trihydrate (388).

—THIOCYANATE: B·HCNS+½H_2O, small sparkling needles, m. p. ca. 100° (284).

—PERCHLORATE: B·$HClO_4+2H_2O$, white crystals, m. p. 150° soluble in water or alcohol. Sol. at 15°, 1 part in 227 parts 4% perchloric acid; it explodes on heating (285) (286).

—FERROCYANIDE: B·$H_4Fe(CN)_6$, white crystals, easily sol. in water; solution turns blue slowly (287).

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* See Appendix, p. 361.

—PLATINOCYANIDE: $(B{\cdot}HCN)_2Pt(CN)_2$, precipitate of microscopic needles (288).

—SILICOTUNGSTATE: $B_4{\cdot}12WO_3{\cdot}SiO_2{\cdot}2H_2O+9H_2O$, amorphous salmon colored precip. (obtainable in dil. 1:16000), holds $2H_2O$ at 120° (158).

—CHROMATE: $B_2H_2CrO_4$, light yellow needles, turning dark in light (54) (289). —DICHROMATE, amorphous precip (54).

—VANADATE: $B{\cdot}HVO_3$, yellow flocc. masses of very fine crystals (290).

—TETRATHIOCYANATO-DIAMMINE CHROMIUM: $B{\cdot}HCNS{\cdot}Cr(NH_3)_2(CNS)_3$, from action of Reinecke's salt on morphine, bright red cryst. precip. insol. cold water, soluble in boiling water, soluble in alcohol (160) (291).

—FORMATE, small prisms, very soluble (292).

—ACETATE: $B{\cdot}C_2H_4O_2+3H_2O$, white crystals grouped in cauliflower form (293). Soluble in 2.25 parts water 25°, 2 parts at 80°; 17.3 parts 95% alcohol, 25°, 2 parts at 60°; in 6.5 parts glycerine, 25°; in 720 parts chloroform, 25° (282). It slowly loses acetic acid, and becomes colored (294) (295). Molecular weight, Klobukow (33), Raoult (31). Solutions deposit morphine crystals slowly (296) (297) (298). $[\alpha]_D=-100.4°$ (abs. alcohol, C=0.012), −77° (water, C=0.025) (299), (see Oudemans (300), Wilhelmy (301)). —MONOCHLOROACETATE, $B{\cdot}C_2H_3O_2Cl$ (78). —DICHLOROACETATE, $B{\cdot}C_2H_2O_2Cl_2+\frac{1}{2}H_2O$, transparent colorless cryst (78). —TRICHLOROACETATE, $B{\cdot}C_2HO_2Cl_3+1\frac{1}{2}H_2O$ (78) (391). —MONOBROMOACETATE (78). —PHENYLACETATE, $B{\cdot}C_8H_5C_2H_3O_2$, m. p. 92° (78).

—BUTYRATE: $B{\cdot}C_4H_8O_2$, rhombic crystals, irregular tetrahedra. Sp. gr. 1.2153, 13°. Soluble in 7 parts water at 12.5°, sol. in cold alcohol. Decomp. below. 100° (54).

—ISOVALERIANATE, rhombic crystals, smelling of valerianic acid, soluble in 4.3 parts water (302) (303).

—OXALATE: $B_2{\cdot}H_2C_2O_4+H_2O$, rhombic crystals, decomp. from 105° up. Sp. gr. 15°=1.2865. Soluble in 21 parts water 12°, nearly insol. in alcohol. Crystal measurements (54). $B{\cdot}H_2C_2O_4+4H_2O$, loses $3H_2O$ in vacuum, anhydrous at 130° (partial decomp.). Thermal data (94).

—LACTATE: $B{\cdot}C_3H_6O_3$, colorless monoclin. plates or needles, from add. of B to hot solution of lactic acid. Crystal measurements; sp. gr. 1.3574. Decomp. 100° to 155°. Sol. in 10 parts water at 13°, in all proportions at 100°, sparingly sol. alcohol, nearly insol. chloroform, ether, olive oil (54). Sol. in 93 parts 85% alcohol at 15.5°; decomp. slowly at 110° (304). —TRICHLOROLACTATE: $B{\cdot}C_3H_3O_3Cl_3+5H_2O$ (78).

—MALATE, from barium bimalate and morphine sulphate, crystals nearly insol. in alcohol (54).

—CITRATE, sol. in 19.5 parts water (303).

—TARTRATE: $B_2{\cdot}C_4H_6O_6+3H_2O$, concentric-grouped needles, effloresce at 20°, anhydrous at 130° (305). Soluble in 9 parts of water (303), sol. in alcohol. —ACID TARTRATE, $B{\cdot}C_4H_6O_6+\frac{1}{2}H_2O$, clusters of flat rectangular prisms, less sol. than neutral salt. Loses water and begins to decomp. about 140° (305). —ANTIMONYL TARTRATE, from adding antimony oxide or oxychloride to morphine tartrate. Rose colored mammilary cryst., sparingly sol. in water, decomp. by boiling water (54).

—URATE, brown prisms, decomp. during recryst. —CYANURATE, colorless prisms; —HIPPURATE, amorphous (279).

—BENZOATE: $B{\cdot}C_7H_6O_2+H_2O$ (?), cryst. from water or alcohol (294).

—PHTHALATE: $B_2{\cdot}C_8H_6O_4+5H_2O$ (?), loses $4H_2O$ over H_2SO_4, the remaining H_2O at 100° (294).

—MELLITATE: $B_3{\cdot}C_{12}H_6O_{12}$, from treatment hot conc. sol. of the acid with B; fine needles, insol. alcohol or ether, more soluble in cold water than in hot (306).

—Picrate, m. p. 163° to 165° corr., sol. in 455 parts water 20° (307).

—Benzene-thiosulphonate: $B{\cdot}C_6H_5SO_2SH$, fine white needles from water (308). —p-Toluene-thiosulphonate, $B{\cdot}C_7H_7SO_2SH$, white cryst. from water (308). —α-Naphthalene-thiosulphonate, $B{\cdot}C_{10}H_7SO_2SH$, cryst. by precip. alc. sol. with ether (308). —β-Naphthalene-thiosulphonate, $B{\cdot}C_{10}H_7SO_2SH$, cryst. by precip. alc. sol. with ether (308). —o-Guaiacol-sulphonate, gray-white hygroscopic powder. Indefin. cryst. from alcohol, ether, acetone; very sol. in water, alcohol (309).

—Acid salt 5, 5′-Dichlorodiphenyl-3, 3′-dicarboxylic acid: $B{\cdot}C_{14}H_8O_4Cl_2$, small nodules from methyl alcohol, m. p. 218° to 219°, decomp. 223° to 225°. Insol. benzene, chloroform, acetone, ether, sparingly sol. methyl and ethyl alcohol, $[\alpha]_D=-30°$ (ethyl alcohol., p=0.20) (310).

—l-Mandelate, sparingly sol. rhombic prisms (311).

—l-Xylonate: $B{\cdot}C_5H_{10}O_6$, needles from alcohol, m. p. 153° (312).

—Benzalsulphite, from treating morphine with SO_2, then benzaldehyde; m. p. 115° (decomp.) (313).

—Meconate, conical, boat-shaped crystals, very sol. in water or alcohol (12) (19). —Bimeconate, see Dott, existence doubtful (314).

—Diallylbarbiturate, needles, m. p. 258°, sol. in hot water, ethyl alcohol, methyl alcohol, acetone, ethyl acetate, insol. in petroleum ether (315) (316). —Phenylethylbarbiturate, white needles, m. p. 250°, sol. in alcohol, diff. sol. water, benzol, acetone (317).

Alloxanmorphinedisulphite: $B{\cdot}C_4H_2O_4N_2{\cdot}H_2SO_3$, crystal. powder from alcohol (318).

—Helianthate: $B{\cdot}C_{14}H_{15}O_3N_3S$, orange plates (319).

—*d*-Oximinocyclohexane-4-Carboxylate (320), sparingly sol. prism rosettes; sol. 30 parts boiling alcohol; $(M)_D=+64.6°$.

Morphine-narcotine salts: (M = Morphine, N = Narcotine).

M-N-Meconate: "Narcophin," "Narphin," $M{\cdot}N{\cdot}C_7H_4O_7+4H_2O$, small white cryst. readily sol. in water or hot alcohol (321) (322) cryst. also with $6H_2O$; at about 140° evolves gas, m. with decomp. at about 168° (323). M-N-Benzoltrisulphonate ($+2H_2O$). (321) M-di-N-Benzoltrisulphonate, $M{\cdot}N_2{\cdot}C_6H_3(SO_3H)_3+2H_2O$, soluble with diff. cold water, sol. hot water or alcohol (322). M-N-Phenoldisulphonate, $M{\cdot}N{\cdot}C_6H_3OH(SO_3H)_2+2H_2O$, diff. sol. cold water, sol. hot water or alcohol (321) (322). M-di-N-Salicyldisulphonate ($+H_2O$) (321). Di-M-N-Salicyldisulphonate, $M_2{\cdot}N{\cdot}C_6H_2OH(COOH)(SO_3H)_2+2H_2O$ (321) (322). M-N-Sulphate, $M{\cdot}N{\cdot}H_2SO_4+4\frac{1}{2}H_2O$ (321) (322). M-N-Hydrochloride, m. p. 200° (324). Uniform yellow short prisms, differing from the hydrochlorides of either of the bases. Easily sol. cold water, with diff. in alcohol, insol. ether (325). M-N-Hydrobromide, contains $2H_2O$, browns and decomp. about 170° (324) (325).

Metallic salts: Potassium morphinate: $C_{17}H_{18}O_3NK+3H_2O$ ($1\frac{1}{2}H_2O$) (73) (326) (327). Barium morphinate $(C_{17}H_{19}O_3N)_2BaO+2H_2O$ (74) (326). Calcium morphinate $(C_{17}H_{19}O_3N)_2CaO+4H_2O$ ($2H_2O$) (326) (328); $(C_{17}H_{18}O_3N)_2Ca$, from alcohol extraction of morphine ground with $Ca(OH)_2$; shining scaly powder, sol. in water or alcohol, sparingly in chloroform, insoluble in ether or benzol. The aqueous solution precip. morphine with ammonium chloride, morphine and $CaCO_3$ with CO_2 (329). Sodium morphinate, Chastaing (330). With one mole NaOH, $[\alpha]_D=-67.5°$, 2 moles, $[\alpha]_D=-71.0°$ (85).

Potassium morphinate carbonate: $(C_{17}H_{18}O_3NK)_2K_2CO_3+2H_2O$ (326).

II. ALKYL HALIDES

—METHIODIDE: $B{\cdot}CH_3I+H_2O$, colorless cryst. powder, easily sol. in water, from which it cryst. in needles (327) (331). M. p. 286° (decomp.) (392). $[\alpha]_D^{25} = -72.9°$ (water, C=1.162)(70). With acetic anhydride it forms a Diacetyl derivative (204).

—METHOCHLORIDE: $B{\cdot}CH_3Cl+2H_2O$, colorless cryst. from water. It loses one H_2O at 100°, the second at 135° to 140°; soluble in 10 parts water, 130 parts alcohol (323). M. p. 285° (decomp.). It gives a violet color with warm H_2SO_4, dark blue with $FeCl_3$. With acetic anhydride, a diacetyl derivative is formed. The PLATINICHLORIDE, $(B{\cdot}CH_3Cl)_2PtCl_4+H_2O$, orange needles, sol. in hot water (327).

—METHOBROMIDE, from shaking morphine many hours with CH_3Br at 50° (332), or from the action of HBr on the methochloride (333); sold as "Morphosan." Colorless needles from water, m. p. 265° to 266°; sol. cold water 1:20, slightly sol. alcohol, chloroform, insol. ether.

—METHOMETHYLSULPHITE, from heating morphine in methyl alcohol with dimethylsulphite at 100°; it precip. crystalline from absol. alcohol by ether (334). Potassium bromide converts it to the methobromide.

—METHOHYDROXIDE: $B{\cdot}CH_3OH+5H_2O$, colorless crystals (335). It is an inner salt, of betaine structure (234). It adds methyl iodide in the absence of alkali to give codeine methiodide.

—ETHIODIDE: $B{\cdot}C_2H_5I+\frac{1}{2}H_2O$, from heating morphine in alcohol with C_2H_5I at 100°. Fine needles from water, sol. with difficulty in absol. alcohol (331).

—ETHOCHLORIDE, needles from water-acetone mixture, m. p. 255° (333).

—ETHOBROMIDE, from treatment of the ethiodide with AgBr, or the ethochloride with KBr; needles from water or alcohol, m. p. 245° (332) (333).

III. ESTERS

FORMYLMORPHINE: $C_{17}H_{18}O_2NOOCH$, prep. by refluxing morphine hydrochloride with sodium formate in 100% formic acid; white cryst powder, m. p. 220° to 225°, sol. in alcohol, chloroform, diff. sol. water or ether; soluble in dilute alkali, gives the $FeCl_3$ reaction (336). It is formed also from the halogenomorphides with sodium formate (337), other prep. methods, Bayer & Co. (338).

α-ACETYLMORPHINE: $C_{17}H_{18}O_2NOOC_2H_3$, prep. by heating morphine with acetic acid or acetic anhydride (217), (221), or, better, by partial hydrolysis of diacetylmorphine with boiling water (222). Cryst. from ether anhydrous or with $2H_2O$, m. p. 187°. Does not give color with $FeCl_3$ (*cf.* Merck (223)). —HYDROCHLORIDE $(+3H_2O)$ (222) $(+\frac{1}{2}H_2O)$, decomp. 280° (223). —PLATINICHLORIDE, $(C_{19}H_{21}O_4N{\cdot}HCl)_2PtCl_4$. —ETHIODIDE $(+\frac{1}{2}H_2O)$ crystals from 85% alcohol. The base gives the following color reactions: H_2SO_4, colorless; conc. HNO_3, red, turning yellow; HIO_3, reduction; Erdmann's reagent, yellow; Fröhde's reagent, violet, turning blue, then yellow.

β-ACETYLMORPHINE, an amorphous solid of decomp. pt. about 180°, obtained by heating morphine 5 hours at 100° with one mole of acetic anhydride. The HYDROCHLORIDE and PLATINICHLORIDE are amorphous. It gives a blue color with ferric chloride (221) (222).

γ-ACETYLMORPHINE, anhydrous crystals from ether. —HYDROCHLORIDE, poorly crystalline. —ETHIODIDE, from 85% alcohol, $C_{19}H_{21}O_4N{\cdot}C_2H_5I+3H_2O$ (217). Danckwortt was unable to obtain this γ-modification (222).

DIACETYLMORPHINE: (Diamorphine, Heroin) $C_{17}H_{17}O_3N(OC_2H_3)_2$, prep. by heating morphine with acetic anhydride (221) (327), or, better, with acetyl chloride (222) (223). Colorless crystals from ether, best recryst. from ethyl acetate. M. p. 173°, b. p. at 12 mm., 272° to 274° (229). $[\alpha]_D^{15} = -166°$

(methyl alcohol, C=1.24) (209). n_D: α=1.56, β=1.60, γ=1.61; specific gravity, 1.32 (55); n_D=1.560 (59). Soluble at 25° in 1,700 parts water, 25 parts alcohol, 2.1 parts chloroform, 70 parts ether (339); sl. sol. in ammonia or soda solution, soluble in alkalies; decomposed by boiling with water. It gives the following color reactions: H_2SO_4, colorless; conc. HNO_3, yellow, turning green, then yellow; H_2SO_4 at 100° for one-half hour, then HNO_3, blood red; $FeCl_3$, no color; HIO_3 not reduced; Erdmann's reagent, pale yellow; Fröhde's reagent, cherry red (222); Marquis' reagent, red-violet, turning blue-violet (120). Comparison with codeine and morphine, Wesenberg (340). The acetyl groups are not replaceable directly by benzoyl groups (233). —HYDROCHLORIDE, $C_{21}H_{23}O_5N \cdot HCl + H_2O$, white cryst. powder, m. p. 231° to 232° (decomp.); soluble in 2 parts of water (25°), soluble in alcohol, insol. ether, or chloroform (282) (339). Magnol test, David (170). The PLATINICHLORIDE and AURICHLORIDE are amorphous (221) (222). —METHIODIDE, needles of m. p. 252°, $[\alpha]_D^{15} = -107°$ (water, C=0.896) (209). —METHOCHLORIDE, white prisms, very sol. in water or alcohol, whose Platinichloride cryst. in yellow needles from water (327). —ETHIODIDE, $C_{21}H_{23}O_5N \cdot C_2H_5I + \frac{1}{2}H_2O$, unstable crystals (217). —ETHOCHLORIDE, crystalline, unstable (217). —o-GUAIACOLSULPHONATE, amorphous, soluble in water or alcohol, insoluble in ether (309). —DIALLYLBARBITURATE, cryst. from ethyl acetate, m. p. 186°, soluble in alcohol, ethyl acetate, chloroform, acetone (315) (316). —ALLYLETHYLBARBITURATE, cryst. of m. p. 67° (341). —DIPROPYLBARBITURATE, and —PHENYLALLYLBARBITURATE, crystalline (341). NITROSONORDIACETYLMORPHINE (188), see normorphine. DIACETYLMORPHINE SULPHONIC ACID, from acetic anhydride-sulphuric acid with morphine below 25°; needles, m. p. above 280°, sol. in water or alcohol, insol. in ether (342).

TRIACETYLMORPHINE: (Aceto-diacetylmorphine), $C_{17}H_{17}O_3N(COCH_3)_3 + H_2O$, prep. by action of acetic anhydride, sodium acetate and zinc dust on morphine. Cryst. from alcohol, m. p. 155°, anhydrous 158° (224) (225). $[\alpha]_D = -180°$. Knorr doubts the existence of this compound (228). By the action of acetic-sulphuric acid on morphine at 85°, another triacetyl morphine, m. p. 206° to 208°, was obtained by Knoll & Co. (230); diff. sol. in water or alcohol, sol. acids, forms a Hydrochloride.

CHLOROACETYLMORPHINE: $C_{17}H_{18}O_3N(COCH_2Cl)$, from partial hydrolysis of di-(chloroacetyl)-morphine; colorless needles from alcohol, decomp. 234° (124) (343).

DI-(CHLOROACETYL)-MORPHINE: (Dichloroheroin), $C_{17}H_{17}O_3N(COCH_2Cl)_2$, from heating anhydrous morphine with chloroacetyl chloride 2½ hours at 100°; cryst. from ether, m. p. 135° (124); decomposes easily to the monochloroacetyl derivative.

α-ACETYLBENZOYLMORPHINE: $C_{17}H_{17}O_3N(COCH_3)(COC_6H_5)$, prep. from α-acetylmorphine and benzoic anhydride at 160°; a crystalline solid, whose amorphous HYDROCHLORIDE is very sol. in water. —PLATINICHLORIDE known. —ETHIODIDE, $C_{25}H_{25}O_5N \cdot C_2H_5I + \frac{1}{2}H_2O$, cryst. from 85% alcohol (217) (233).

ACETYLBUTYRYLDIMORPHINE: $C_{17}H_{15}O_3N(OC_2H_3) \cdot C_{17}H_{18}O_3N(OC_4H_7)$, from heating morphine with acetic and butyric acid mixture. —DIHYDROCHLORIDE ($+8H_2O$), crystalline (233).

DIPROPIONYLMORPHINE: $C_{17}H_{17}O_3N(OC_3H_5)_2$, from morphine and propionic anhydride at 85°; amorphous, very sol. in ether, alcohol, or chloroform. The HYDROCHLORIDE and PLATINICHLORIDE are amorphous (327) (*cf.* Merck (223)).

α-BUTYRYLMORPHINE: $C_{17}H_{15}O_3N(OC_4H_7)$, from heating 1 part morphine with 2 parts butyric acid at 130°; crystals from ether; gives no color with $FeCl_3$. —HYDROCHLORIDE, crystalline. —PLATINICHLORIDE (233), and —ETHIODIDE (217) are known.

β-BUTYRYLMORPHINE: $C_{17}H_{18}O_3N(OC_4H_7)$, formed with the α-compound. Amorphous, colored by $FeCl_3$ (233).

DIBUTYRYLMORPHINE, amorphous, giving amorphous HYDROCHLORIDE, PLATINICHLORIDE, and ETHIODIDE (233).

SUCCINYLMORPHINE: $C_{17}H_{18}O_3N(COC_2H_4COOH)+4H_2O$, cryst. from 80% alcohol, insol. in water, ether, benzol, gives no color with $FeCl_3$. —HYDROCHLORIDE, crystalline. —PLATINICHLORIDE is known (218).

CAMPHORYLMORPHINE, amorphous, giving an amorphous HYDROCHLORIDE and PLATINICHLORIDE (218).

BENZOYLMORPHINE: $C_{17}H_{18}O_3N(OC_7H_5)$, from benzoic acid and morphine at 160°, isolated as the cryst. HYDROCHLORIDE or PLATINICHLORIDE (233), also from the action of benzoyl chloride; needles from alcohol, m. p. 145°. —HYDROCHLORIDE, m. p. 176° to 177° (decomp.) (223).

DIBENZOYLMORPHINE: $C_{17}H_{17}O_3N(OC_7H_5)_2$, from the action of benzoyl chloride on morphine at 100° (232), or benzoic anhydride at 130° (233). Large prisms from alcohol, m. p. 188° to 190.5°; identical with Polstorff's (231) tribenzoylmorphine. —HYDROCHLORIDE ($+H_2O$) (223). —PLATINICHLORIDE, amorphous. —ETHIODIDE ($+\frac{1}{2}H_2O$), cryst. from 85% alcohol (217). The base, heated in dilute alcohol, gives monobenzoylmorphine and benzoic acid; with conc. H_2SO_4 it gives benzoic acid and apomorphine; Fröhde's reagent, purple-red turning yellow; vanadium-sulphuric acid, weak red (222).

DIBENZOYLACETYLMORPHINE, from dibenzoylmorphine with acetic-sulphuric acid at 85°; m. p. 166° to 168°, sol. in warm alcohol or benzol, nearly insol. in water (230).

CARBOMETHOXYMORPHINE, from methylchlorocarbonate and potassium morphinate (390); m. p. 120°, soluble in benzol, alcohol, ether, chloroform, ethyl acetate, insol. in petroleum ether. —SULPHATE $(C_{17}H_{18}O_3N(COOCH_3))_2H_2SO_4$, m. p. 225°. —HYDROCHLORIDE, crystalline. —PLATINICHLORIDE (344), yellow cryst. precip.

CARBETHOXYMORPHINE: $C_{17}H_{18}O_3N(COOC_2H_5)$, m. p. 113°. —SULPHATE, and —HYDROCHLORIDE are known. —PLATINICHLORIDE, crystallizes from alcohol. —OXALATE ($+2H_2O$), cryst. from dil. alcohol (344). Gadamer (345) purified the base through the bitartrate (cryst. from alcohol, m. p. 121° to 122°, decomp., $[\alpha]_D=-51.4°$ (water)) and obtained the m. p. 123° to 124° $[\alpha]_D=-143.7°$ (alcohol). As a by-product of the reaction, $C_{17}H_{16}O_2N(COOC_2H_5)_3$ $[\alpha]_D=-188.8°$ (alcohol) was obtained.

CARBOPROPOXYMORPHINE, isolated as the HYDROCHLORIDE, and PLATINICHLORIDE, $(C_{21}H_{25}O_5N\cdot HCl)_2PtCl_4+2H_2O$. The Carbisopropoxy- and Carbamoxy-compounds are also known (223).

ACETYLCARBOMETHOXYMORPHINE, from α-acetylmorphine with methylchlorocarbonate and alkali; coarse prisms or needles, m. p. 168° (346) (347). ACETYLCARBETHOXYMORPHINE, needles from absol. alcohol, m. p. 150°. —HYDROCHLORIDE, needles, decomp. 185°. —PLATINICHLORIDE, orange needles, m. p. 210° (223) (346) (347). ACETYLCARBOPROPOXYMORPHINE, colorless needles, m. p. 120° (346) (347).

ETHOXYACETYLMORPHINE, cryst. clumps, m. p. 155°, soluble in alcohol, ether, benzol, chloroform, alkali. —HYDROCHLORIDE, needles m. p. 186° (348). DI(ETHOXYACETYL)MORPHINE, from morphine with ethoxyacetyl anhydride; an oil, soluble in alcohol, ether, benzol. —HYDROCHLORIDE, leaflets, sol. in water, alcohol, decomp. 142° (348). PHENOXYACETYLMORPHINE, cryst. warts from ether, decomp. ca. 125°, sol. in alcohol, ether, benzol (348).

p-ACETOXYBENZOYLMORPHINE: $C_{26}H_{25}O_6N$, needles from ethyl acetate, sinter 225°, decomp. 232°; soluble at 15° in 60 to 70 parts of ethyl acetate, less sol. in methanol or ethanol. —HYDROCHLORIDE, prisms. —METHOCHLORIDE, prisms, sol. in 75 parts of water (349). p-CARBOMETHOXYBENZOYLMORPHINE, $C_{26}H_{25}O_7N$, prisms from alcohol, decomp. 175° to 176°. —HYDROCHLORIDE ($+CH_3OH$, or

C_2H_5OH) browns 165°, decomp. 190°, soluble in 2.5 parts methyl alcohol, 4 parts ethyl alcohol. Hydrolyzes to the p-HYDROXYBENZOYL derivative (349). p-HYDROXYBENZOYLMORPHINE, $C_{24}H_{23}O_5N$, leaflets from 22 parts of 50% alcohol; browns 230°, decomp. 237°; –HYDROCHLORIDE, –METHOBROMIDE are cryst. (349).

DI-α-BROMOISOVALERYLMORPHINE, yellow powder, sinters 61°, decomp. 133°, soluble in ether, alcohol, chloroform, benzol (343).

BENZENESULPHONYLMORPHINE: $C_{22}H_{23}O_5NS$, from morphine with benzenesulphonyl chloride, 2 hrs. at 100°. Cryst. from ether, m. p. 165°, insoluble in alkali. Its BENZENE SULPHONATE cryst. from water in needles, m. p. 140° (124).

MORPHINE SULPHURIC ACID: $C_{17}H_{18}O_2NOSO_2OH+2H_2O$, white silvery needles from hot water. Prep. by reaction of potassium morphinate 8 to 10 hours with potassium pyrosulphate at room temp. Very diff. sol. in cold water, alcohol, ether, sol. in 100 parts hot water, sol. in alkali; not precip. by $BaCl_2$, gives no $FeCl_3$ reaction. Heated with dil. HCl it gives morphine and H_2SO_4(350).

IV. ETHERS

Morphine ethers are prepared by reaction of alkali morphinate with alkyl halides (351) (352), alkyl sulphates (353), alkyl nitrates (354), trialkyl phosphates (355), or of morphine with trialkyl phenylammonium hydroxide (240, 356), or diazoalkanes (236). See Codeine, preparation. Reuter (357) recommends alkylation in the presence of reducing agents, as alkyl oxalates, anhydrous salts of pyrogallic acid, sulphites, etc. in order to minimize oxidation of morphine in alkaline solution.

—METHYL ETHER, see Codeine.

—METHYL ETHER, Heterocodeine (245), $C_{18}H_{21}O_3N$, by methylation of the alcoholic hydroxyl group of morphine. Morphine methoxymethyl (phenolic) ether-N-oxide is methylated with dimethyl sulphate, and the methoxymethyl group split off and the N-oxide reduced by sulphurous acid. Cryst. from alcohol, m. p. 242°. Soluble in alkali; blue $FeCl_3$ reaction; it methylates to codeine methyl ether. Its HYDROCHLORIDE ($+2H_2O$) cryst. in prisms from water, m. p. 102°. The METHOCHLORIDE, white cryst. from dil. alcohol, m. above 270°.

—DIMETHYL ETHER (245), see Methyl codeine.

—ETHYL ETHER (Ethylmorphine, Codethyline), $C_{19}H_{23}O_3N+H_2O$, prep. by treatment of morphine with ethyl iodide in the presence of $NaOC_2H_5$ (351) (358); with alkali ethyl sulphate, Knoll (359); with ethyl bromide instead of ethyl iodide a yield of 85% to 90% is claimed (352); ethylation has also been carried out with sodium ethylate and diethyl sulphate (237), triethyl phosphate (360), or ethyl nitrate (361). E. Merck describes ethylation of morphine-N-oxide, and subsequent reduction of codethyline-N-oxide to codethyline (251). Use of ethyl-p-toluenesulphonate, Rodionov (240). Prismatic cryst. from water, m. p. 93°; n_D: $\alpha=1.55$, $\beta=1.58$, $\gamma=1.65$; sp. gr. (hydrate), 1.29 (55). Soluble 0.35 parts in 100 of water (ord. temp.), 149 parts in 100 of alcohol at 15°, soluble in ether or chloroform, with difficulty in benzol, insoluble in ligroin (223) (362). B. p. at 12 mm., 260° to 262°; unaffected by long heating with acetic anhydride (229). —HYDROCHLORIDE (Dionin), $C_{19}H_{23}O_3N\cdot HCl+H_2O$, white microcrystalline powder, m. p. 123° to 125° (decomp.), bitter in taste. Loses H_2O at 56° over P_2O_5, regains it in air (363). Soluble 14 parts in 100 of water at 15°, in alcohol 73 parts in 100; insoluble in ether or chloroform. It gives with most alkaloid reagents the same reactions as codeine hydrochloride. Detected by Dragendorff's reagent in dilution 1:100,000, Bouchardat's 1:10,000, Mayer's 1:5,000, Scheibler's 1:1,000 (223) (362). Marquis' reagent gives a permanent deep blue (120). See also David's test (170). —SULPHATE $(C_{19}H_{23}O_3N)_2H_2SO_4+5H_2O$, m. p. 207°, sol. at 15.5° in 9.5 parts water, 89 parts of 90% alcohol (364). —DIALLYLBARBITURATE, crystals of m. p. 285°, very soluble in organic media except petroleum

ether (315) (316). —ALLYLETHYLBARBITURATE, cryst. of m. p. 67° (341). Other barbiturates mentioned. —PHENYLETHYLBARBITURATE, white needles of m. p. 87°, soluble with diff. in water, sol. in organic media (299) (317). —o-GUAIACOLSULPHONATE, white cubical cryst. from conc. aqueous solution (309). —METHIODIDE, $C_{19}H_{23}O_3N \cdot CH_3I$; degrades to ethylmorphimethine, m. p. 132° (351). —METHOBROMIDE, $C_{19}H_{23}O_3N \cdot CH_3Br + H_2O$, from the quaternary hydroxide with HBr; prisms, m. p. (anhydrous) 267° to 268°. Easily sol. water, with difficulty in methyl or ethyl alcohol, insol. acetone, chloroform, ether (365). —ETHIODIDE, needles soluble in warm water or hot alcohol. Degradation (366). —ETHOBROMIDE, white needles from water. Cryst. with three or four molecules of crystal-water. Prep. from morphine with ethyl bromide and alkali. M. p. (anhyd.) 225°; sol. in water, methyl, or ethyl alcohol, slightly in acetone or chloroform, insol. in ether (365). —OXIDE, $C_{19}H_{23}O_4N$, needles from water, m. p. 220° to 221°; —Sulphate, Hydrochloride, Nitrate (196). —DIHYDROCODETHYLINE, see under Dihydromorphine. NITROETHYLMORPHINE (367), $C_{19}H_{22}O_5N_2$, from nitration of ethylmorphine, yellow cryst., m. p. 166° to 167°; it reduces to aminoethylmorphine, m. p. 115° to 116°. The acetylamino compound forms a yellow hydrochloride. Diacetylaminoethylmorphine has the m. p. 156°.

MORPHINE-β-CHLOROETHYL ETHER: $C_{19}H_{22}O_3NCl$, prep. from morphine with β-chloroethylbenzenesulphonate; m. p. 75° to 76°, solidifies and remelts at 105° (decomp.). Anhydrous, m. p. 118° to 120°. —HYDROCHLORIDE ($+H_2O$), m. p. 150° to 151°, m. p. anhydrous 166° to 168°. Recryst. from acetone cont. a little water or methyl alcohol. —SULPHATE (neutral) needles from alcohol, m. p. 115° to 120° (foaming), solidifies and remelts at 235° to 240° (decomp.). —PHOSPHATE (primary), cryst. slowly from methyl alcohol on addition of acetone, decomp. 110°. —HYDRIODIDE, yellow cryst. from water cont. CH_3OH and HI; m. p. 212° to 213°, slightly sol. in water, more sol. in CH_3OH. —OXALATE (neutral), from methyl alcohol by addition of ether, needles of m. p. 85° to 87°. Moderately sol. in water (368).

MORPHINE β-BROMOETHYL ETHER, m. p. 135° to 136° (gas evol.), solidifying and remelting at 185° to 187°. Its HYDROCHLORIDE (impure) melts at 210° to 230° (368).

MORPHINE n-PROPYL ETHER: $C_{17}H_{18}O_2N(OC_3H_7) + \frac{1}{2}H_2O$, m. p. 69° to 70°, prep. from sodium morphinate and propyl-p-toluenesulphonate. Isolated as the hydrochloride ($+H_2O$), decomp. 146° to 153° (hydrated form m. p. 111° to 114°) (241). Mering (352) used propyl bromide for the prep. of this ether.

—β-β′-DICHLOROISOPROPYL ETHER, m. p. (impure) 115°. —HYDROCHLORIDE, m. p. 147° (368).

—n-BUTYL ETHER, not crystalline, isolated as the HYDROCHLORIDE, $C_{17}H_{18}O_2N(OC_4H_9) \cdot HCl + H_2O$, precip. from alcohol by ether, m. p. 101° to 104°, m. p. anhydrous, 119° to 122° (241).

—ALLYL ETHER (Allylmorphine): $C_{17}H_{18}O_2N(OCH_2CH{=}CH_2) + \frac{1}{2}H_2O$, prep. by allylation of sodium morphinate with allylbenzenesulphonate (368) (369), or allyldimethylphenylammonium bromide (autoclave) (316), isolated as the Hydrochloride or Sulphate. Free base, colorless cryst., m. p. 67° to 68°; sol. in methyl, ethyl alcohol, acetone, ether, chloroform, benzol; insol. in water or petroleum ether. —HYDROCHLORIDE ($+H_2O$), m. p. 130° to 132°; m. p. anhydrous, 152° to 153°; $[\alpha]_D^{19}$ (hydrated) $= -85.69°$ (water, p = 6.08). —SULPHATE (neutral) $+3H_2O$, colorless needles, 167° to 168°; it cryst. from alcohol anhydrous, m. p. 172° to 173°; sol. in water, sparingly in methyl or ethyl alcohol; insol. acetone, ether. —SULPHATE (acid), recryst. from alcohol, m. p. 202° to 203°; very soluble in water. —PHOSPHATE (neutral), brown powder, m. p. 100°; by recryst. from alcohol-acetone-ether mixture it is converted to the primary phosphate. —PHOSPHATE (primary), recryst. from acetone containing a little water, m. p. 186°;

sparingly sol. in methyl, ethyl alcohol, or acetone; insol. in ether. —OXALATE (neutral) cryst. from alcohol, m. p. 130°, solidifying and melting again at 203°. —HYDRIODIDE, recryst. from water cont. HI; yellow anhydrous crystals, m. p. 225° to 226°. Sol. in methyl alcohol, sparingly in acetone or water (368). —DIALLYLBARBITURATE, crystals, soluble in methyl, ethyl alcohol, acetone, or chloroform (315) (316).

—BENZYL ETHER (Benzylmorphine): $C_{17}H_{18}O_2N(OCH_2C_6H_5)$, prep. by refluxing 100 parts morphine with 23 parts $NaOC_2H_5$ and 43 parts benzyl chloride in 20 parts absol. alcohol; precip. as the Hydrochloride in nearly theoret. yield (389). Base is very slightly sol. in water, easily in alcohol, ether, or benzene; gives no ferric chloride reaction; salts with organic acids are amorphous (239). —HYDROCHLORIDE (Peronin), $C_{24}H_{23}O_3N{\cdot}HCl + H_2O$ (370) (*cf.* Merck (223)), white microcrystalline powder, sol. in 133 parts water at 15°, in 218 parts 95% alcohol, 390 parts chloroform, 100 parts methyl alcohol. Sol. with diff. in acetone, ether, amyl alcohol, dilute mineral acids. Boiling with dil. HCl splits it to morphine and benzylchloride. Color reactions: with conc. H_2SO_4, yellow, on warming turns brown-red, then red, finally dark red; H_2SO_4 and HNO_3, dark red-brown; conc. HNO_3, pale yellow; ammonium molybdate and conc. H_2SO_4, violet, turning brown, then permanent blue (371). With Marquis' reagent, permanent red-violet (120).

—METHOXYMETHYL ETHER: $C_{17}H_{18}O_2N(OCH_2OCH_3)$, prep. by treatment of dry sodium morphinate in chloroform with $ClCH_2OCH_3$. Colorless needles, m. p. 94° to 96°, sol. in alcohol, ether, chloroform, with difficulty in water, insoluble in alkali; decomposed by acids, especially H_2SO_3, to morphine. —SULPHATE ($+10H_2O$), crystalline. —METHIODIDE, needles from alcohol, m. p. 225° (decomp.). —METHYL ETHER METHIODIDE, cryst. from 80% alcohol, m. p. 253° (decomp.). —METHYL ETHER METHOCHLORIDE, decomp. 200° (245) (372) (373).

—CARBOXYMETHYL ETHER (Morphoxyl acetic acid): $C_{17}H_{18}O_2NOCH_2COOH$, prep. from morphine in alcoholic KOH with $ClCH_2COOK$; needles from dil. alcohol, decomp. ca. 192°; soluble in water, insol. in ether. The POTASSIUM SALT cryst. in needles (374).

—QUINOLINE ETHER: $C_{17}H_{18}O_2NOC_9H_6N$, prep. by heating morphine with 2-chloroquinoline at 250° to 260°. Cryst. from alcohol, in starry groups of prisms, m. 158°; insol. in alkali, no $FeCl_3$ reaction. The HYDROCHLORIDE does not cryst. well. —NEUTRAL SULPHATE ($+3H_2O$), cryst. from water, m. p. 257° (decomp.), $[\alpha]_D = -66.46°$ (dil. HCl). The CHROMATE is a yellow precipitate. —TARTRATE, prisms from alcohol melting with decomp. at 98°. —PICRATE, yellow crystals, m. p. 250° to 252° (decomp.) (387).

DIMORPHINE ETHYLENE ETHER (Dicodethine): $C_{17}H_{18}O_2NOCH_2CH_2OC_{17}H_{18}O_2N$, prep. from sodium morphinate and ethylene dibromide, needles from dil. alcohol, m. p. 188°. —HYDROCHLORIDE, crystalline (223) (351).

DIMORPHINE PENTAMETHYLENE ETHER (Pentamethylene dimorphine), from morphine, diiodopentane and alkali; amorphous powder, m. unsharp 70° to 100°, somewhat soluble in water (375).

MORPHINE GLUCOSIDE (242): $C_{17}H_{18}O_3N{\cdot}C_6H_{11}O_5{\cdot}H_2O$, prep. by reaction of morphine in alkaline solution with acetobromoglucose, and saponification of the tetraacetyl compound; or directly when strong alkali is used; bitter-tasting needles from 50% alcohol, m. p. unsharp 183° to 193°. It gives no crystalline salts, insol. in alkali, gives no $FeCl_3$ test, and does not reduce Fehling's solution. MORPHINE TETRAACETYLGLUCOSIDE cryst. from dil. alcohol in white needles, m. p. 154° to 156°, cryst. HYDROCHLORIDE, m. p. about 220° (decomp.).

V. DIHYDROMORPHINE AND ITS DERIVATIVES

DIHYDROMORPHINE: $C_{17}H_{21}O_3N + H_2O$, prep. by catalytic reduction of morphine: 10 g. of morphine hydrochloride in 250 c. c. of water is added to 0.1 g. of colloidal palladium in 10 c. c. of water, and shaken with H_2 until the calculated amount is absorbed; palladium is precip. out by addition of 1 c. c. of normal H_2SO_4. From the filtrate, made alkaline with Na_2CO_3, the base separates as needles. Recryst. from methyl or ethyl alcohol, m. p. 155° to 157° (decomp.); large prisms from acetone or chloroform. It gives reactions like morphine with Husemann's, Marquis', or Fröhde's reagents, or $FeCl_3$, and reduces $AgNO_3$ (246) (247) (248). Crude opium extract may be hydrogenated, and dihydromorphine isolated from this (250). A nickel suboxide catalyst has also been used for the preparation (249). Red. with Pt in formic acid, Zimmer & Co. (376). Prep. by demethylation of tetrahydrothebaine. (See Boehringer (255).) Action of ozone, Speyer (256). (See Dihydrocodinal, p. 199.) Prep. from dihydrocodeine, Mannich (253). —HYDROCHLORIDE (Paramorfan): $C_{17}H_{21}O_3N \cdot HCl$, prisms, sol. in water, sol. with diff. absol. alcohol. —HYDRIODIDE, sol. in water, diff. sol. alcohol, browns 270°, melts 275°. —PICRATE, yellow prisms, m. p. 139° (250). —DIALLYLBARBITURATE, m. p. 125°, sol. hot water, alcohol, acetone, chloroform (316) (377).

DIACETYLDIHYDROMORPHINE: $C_{21}H_{25}O_5N$, needles, m. p. 165° to 167°, diff. sol. water. —HYDROCHLORIDE, sol. in water (185) (252).

DIHYDROMORPHINE METHYL ETHER, methylation methods, Knoll (252), Merck (251). (See Dihydrocodeine.)

DIHYDROMORPHINE DIMETHYL ETHER (Dihydrocodeine methyl ether), by catalytic reduction of codeine methyl ether. Isolated as the Hydrochloride, $C_{19}H_{25}O_3N \cdot HCl + 3H_2O$, plates from water, m. p. 116° (245). Identical with tetrahydrothebaine (254). (See Dihydrocodeine methyl ether, p. 198, Tetrahydrothebaine, p. 304.)

DIHYDROMORPHINE ETHYL ETHER (Dihydrocodethyline), an oil, sol. in alcohol, sol. with diff. water. —ACID CITRATE, cryst. from alcohol, m. p. 158° to 159°, $C_{25}H_{33}O_{10}N + H_2O$ (252). Ozonization, Speyer (207), see ozodihydroethylmorphine.

DIHYDROMORPHINE-N-OXIDE: $C_{17}H_{21}O_4N$, cryst. from alcohol in plates, sinter 257°, decomp. 261° (258).

α-DIHYDROMORPHINE SULPHONIC ACID: $C_{17}H_{20}O_3NSO_3H$, prep. by catalytic reduction of morphine sulphonic acid; fine scales from 50% alcohol; darkens 338° to 350°, decomp. above 360°. It is also obtained by reduction of morphine-N-oxide sulphonic acid, or by treating dihydromorphine-N-oxide sulphonic acid with SO_2. It methylates to dihydrocodeine sulphonic acid methohydroxide (p. 198). A second ("ordinary") Dihydromorphine sulphonic acid, $C_{17}H_{20}O_3NSO_3H$, is obtained when morphine-N-oxide sulphonic acid is catalytically reduced in the form of its sodium salt. It darkens 301° to 306°, decomp. above 360°, and differs in solubility and crystal form from the α- compound (258).

DIHYDROMORPHINE-N-OXIDE SULPHONIC ACID: $C_{34}H_{44}N_2S_2O_{15}$, prep. by the action of acetic anhydride-sulphuric acid on dihydromorphine-N-oxide. Prisms, darkening 334°, decomp. above 360° (258), reduces with SO_2 to α-dihydromorphine sulphonic acid.

CYANODIACETYLDIHYDRONORMORPHINE: $C_{21}H_{22}O_5N_2$, from the action of BrCN on diacetyldihydromorphine; precip. from alcohol by petroleum ether, silky needles, m. p. 138° to 139°, very sol. in alcohol (185) (186). CYANODIHYDRONORMORPHINE, $C_{17}H_{18}O_3N_2$, by hydrolysis of the diacetyl compound. Leaflets from alcohol, m. p. 291° (186) (257). DIHYDRONORMORPHINE, prep. by hydrolysis of cyanodihydronormorphine, or by catalytic reduction of normorphine hydrochlo-

ride. Needles, very slighly soluble in organic media, somewhat sol. in hot water, m. p. 267°; –Hydrochloride, $C_{16}H_{19}O_3N \cdot HCl$, colorless needles, m. p. 303°; –Platinichloride, yellow cryst. precip. (186) (257).

CHLORODIHYDROMORPHIDE (253), page 226.

VI. MISCELLANEOUS MORPHINE DERIVATIVES

BROMOMORPHINE: $C_{17}H_{18}O_3NBr + \frac{1}{2}H_2O$, prep. by treatment of diacetylmorphine with bromine, followed by hydrolysis. Prisms from alcohol, soluble in alkali. —HYDROCHLORIDE ($+3H_2O$), white needles from water. —HYDROBROMIDE ($+3H_2O$), fine white needles, charring at 221° (213). —METHIODIDE ($+H_2O$), colorless prisms from water, m. p. 252°. BROMOMORPHINE METHOHYDROXIDE reacts with methyl iodide (*cf.* morphine methohydroxide) to give bromocodeine methiodide (212). DIACETYLBROMOMORPHINE, $C_{17}H_{16}O_3NBr(CO\text{-}CH_3)_2$, prisms from methyl alcohol, m. p. 208°; –Methiodide ($+1\frac{1}{2}H_2O$) m. p. 200° (212); –Hydrobromide, needles (213).

TETRABROMOMORPHINE, $C_{17}H_{15}O_3NBr_4 + 2H_2O$, from the action of bromine on morphine hydrobromide (211), or from morphine with HBr and H_2O_2 (213). Occurs in two forms: α-hydrobromide, cryst. of m. p. 218°; β-hydrobromide, m. p. 178°. α-Sulphate ($+H_2O$), Oxalate and Ba salt are also known.

NORMORPHINE: $C_{16}H_{17}O_3N + 1\frac{1}{2}H_2O$, prep. by hydrolysis of cyanonormorphine (*cf.* Speyer and Walther (188)); white needles, insol. ether, chloroform, diff. sol. alcohol, hot water, m. p. 272° to 273° (263° to 264°). —HYDROCHLORIDE ($+H_2O$) decomp. 305°. —PLATINICHLORIDE ($+3H_2O$) decomp. 230° to 231°. —SULPHATE ($+3H_2O$), crystalline. —PICRATE, poorly cryst. TRIACETYL DERIV., cryst. from alcohol, m. p. 164°. DIBENZOYL DERIV., m. p. 208°. PHENYLTHIOUREA DERIV., $C_{16}H_{14}O(NCSNHC_6H_5)(OH)_2$, m. p. 245° (185) (186). With methyl iodide and alkali, normorphine gives codeine methiodide. O-METHYLNORMORPHINE, see Norcodeine. O-ETHYLNORMORPHINE (Norcodethyline) $C_{16}H_{16}O_2NOC_2H_5$, from hydrol. of cyanonormorphine ethyl ether, m. p. 156°; –Hydrochloride ($+2H_2O$) needles from water, m. p. 295°; –Platinichloride, m. p. 229°; Nitroso deriv., m. p. 205° (375). O-PENTAMETHYLENEDINORMORPHINE, $C_{16}H_{16}O_2NO(CH_2)_5OC_{16}H_{16}O_2N$, m. p. 132° to 133°; –Dihydrochloride, m. p. 235° to 240°; –Platinichloride, decomp. 240° to 250°; Dinitroso compound, m. p. 145° to 150°, may be reduced to the corresponding Dihydrazine of m. p. 140° to 145° (375). O-ALLYLNORMORPHINE, $C_{16}H_{16}O_2NOC_3H_5$, cryst. from alcohol, m. p. 164°; –Hydrochloride ($+H_2O$), needles from water, m. p. 240°; –Platinichloride ($+H_2O$), darkens 200°, decomp. 250°; Nitroso derivative, m. p. 176° (375). O-ISOAMYLNORMORPHINE, $C_{16}H_{16}O_2NOC_5H_{11}$, m. p. 100°; –Hydrochloride, from alcohol-ether, m. p. 278°; Nitroso compound, m. p. 186° (185). O-p-NITROBENZYLNORMORPHINE, $C_{16}H_{16}O_2NOCH_2C_6H_4NO_2$, colorless cryst. from alcohol, m. p. 180°; –Hydrochloride, decomp. 297° (378). O-p-AMINOBENZYL-N-CARBAMINONORMORPHINE, $C_{16}H_{15}O_2(NCONH_2)(OCH_2C_6H_4NH_2)$, from Sn–HCl reduction of the nitrobenzylcyano compound; cryst. from alcohol, m. p. 297° (378). NITROSONORMORPHINE, $C_{16}H_{16}O_4N_2$, needles from alcohol, decomp. 267°. Obtained by saponification of nitrosonordiacetylmorphine (cryst. from dil. alcohol, m. p. 202° to 203°) which results when diacetylmorphine is treated with nitrous acid (188). CYANONORMORPHINE, $C_{17}H_{16}O_3N_2$, prep. by treatment of diacetylmorphine with CNBr (185) (186) or CNCl (187) followed by hydrolysis. Cryst. powder from alcohol, m. p. 295° to 296°. The Diacetyl derivative (cyanonorheroin) cryst. from alcohol, m. p. 240°; Cyanomonobenzoylnormorphine, cryst. from alcohol, m. p. 265°. Sodium derivative, $C_{17}H_{15}O_3N_2Na$ (375). Methylation results in cyanonorcodeine; –Ethyl ether (cyanonorcodethyline) m. p. 225° to 226°; –Allyl ether, m. p. 221°; Pentamethylenedi-(cyanonormorphine),

m. p. 226° to 230° (375); -Isoamyl ether, m. p. 225° (185); -p-Nitrobenzyl ether, cryst. from alcohol, m. p. 229° (378). DIHYDRONORMORPHINE (257), see under Dihydromorphine.

MORPHINE-N-OXIDE: $C_{17}H_{19}O_4N$, prep. by the action of 30% H_2O_2 on morphine. Prisms from 50% alcohol, m. p. 274° to 275°. —NITRATE ($+1\frac{1}{2}H_2O$), m. p. 206° to 208°; on drying, this is converted to a dimolecular product, $C_{34}H_{38}O_{13}N_4$ (196) (379). (*Cf.* Mossler and Tschebull (380).) The action of sulphuric acid-acetic anhydride converts morphine-N-oxide to a dimolecular product, MORPHINE HYDRATE OXIDE SULPHONIC ACID, $C_{34}H_{40}O_{15}N_2S_2$. needles of m. p. 280° (381) (382), which with SO_2 goes to morphine sulphonic acid hydrate; structure, Freund (379), Speyer and Becker (258). ACETYLMORPHINE-N-OXIDE, from action of H_2O_2 on diacetylmorphine (one acetyl group is hydrolyzed off). Cryst. with $3H_2O$, m. p. 205°, $[\alpha]_D = -144°$ (alcohol) (383).

MORPHINE HYDRATE SULPHONIC ACID: $C_{17}H_{21}O_7NS$, prisms, sol. in water, m. p. above 300°; reduces catalytically to dihydromorphine sulphonic acid; it loses one molecule of water at 170° to 180° to give a product analyzing for morphine sulphonic acid (258) (379).

DIMORPHENYLMETHANE, from condensation of morphine with formaldehyde in the presence of HCl; amorphous, sol. with diff. in water, sol. in alcohol, alkali, soda, sparingly in benzol or chloroform. —HYDROCHLORIDE, sol. in water or 90% alcohol (384).

DESOXYMORPHINE (70), prep. in very small yield by reduction of chloromorphide with tin and hydrochloric acid. —HYDROCHLORIDE, $C_{17}H_{19}O_2N \cdot HCl + 1\frac{1}{2}H_2O$, needles from water, $[\alpha]_D^{27} = +140.3°$ (C=2.363). A desoxymorphine is mentioned by Wright (385).

DIHYDRODESOXYMORPHINE, $C_{17}H_{21}O_2N$. Prep. by reduction of α-chloromorphide in methyl alcohol in the presence of palladium-barium sulphate catalyst; white cryst. from ethyl acetate, m. p. 184.5° to 185.5° (decomp.). It is very sol. in most organic media except ligroin; it sublimes in high vacuum at 140°. $[\alpha]_D^{30} = -87.01°$ (methanol, C=1.586). It methylates to dihydrodesoxycodeine-D (m. p. 107°) (386).

TETRAHYDRODESOXYMORPHINE, $C_{17}H_{23}O_2N$, prep. by demethylation of tetrahydrodesoxycodeine (p. 246) with hydriodic acid; white cryst. powder from methyl acetate; sol. in most organic media, but decomp. rapidly in solution. M. p. 241° to 243°, $[\alpha]_D^{24} = -77.5° \pm 5°$ (methyl acetate, C=0.923). —HYDROCHLORIDE, white cryst. from absol. alcohol-ether, m. p. 260° to 262°. —METHIODIDE, m. p. 269° to 271°, white cryst. from alcohol. —HYDRIODIDE, cryst. from water. —SALICYLATE, cryst. from alcohol. The base methylates to tetrahydrodesoxycodeine (393).

2-NITROSOMORPHINE: $C_{17}H_{18}O_4N_2 \cdot H_2O$, prep. by treating a suspension of morphine hydrochloride in cold water with nitrous acid (gas). Orange-red needles from alcohol, m. p. 225° (decomp.). Diff. sol. in most media, sol. in hot xylene; stable toward boiling acids or alkalies. SODIUM SALT, garnet-colored needles from 90% alcohol, begins to decomp. at 220°, unmelted at 300°. The SILVER SALT, is a nearly black powder, m. 181° to 182° (decomp.); methylation was unsuccessful. AMMONIUM SALT, dark red leaflets decomp. 173° to 174°. The HYDROCHLORIDE, lemon-yellow needles from dil. HCl, darkens at 200°, m. p. 248° (decomp.) (124). The base and salts exhibit polymorphism.

2-AMINOMORPHINE: $C_{17}H_{20}O_3N_2 \cdot H_2O$, prep. by reduction of the 2-nitrosomorphine; quadratic plates from alcohol, m. p. 258°, sol. with diff. water, alcohol, chloroform, insol. in benzol or ether; sol. in alkali. The DIHYDROCHLORIDE cryst. from absol. alcohol, $[\alpha]_D = -90°$ (20% aqueous solution), gives a violet ferric chloride reaction. The PICRATE cryst. in yellow needles from water, decomp. 172° (124).

DIAZOMORPHINE ANHYDRIDE results when aminomorphine is diazotized; the yellow HYDROCHLORIDE decomp. ca. 98°. It couples slowly in alkaline solution with phenols, giving insol. highly-colored products (124).

2-HYDROXYMORPHINE is obtained from diazomorphine as the amorphous HYDROCHLORIDE (124).

MORPHINE AZOBENZENE: $C_{23}H_{23}O_3N_3$, from morphine with diazotized aniline, orange precip. which cryst. on slow evaporation of the alcoholic solution; m. p. 175° (decomp.). It reduces to 2-aminomorphine with $SnCl_2$ (124).

MORPHINE QUINITROL is formed together with nitrosomorphine by the action of nitrous acid on morphine; the NITRATE $C_{17}H_{18}O_6N_2 \cdot HNO_3 + H_2O$, cryst. as orange-yellow prisms. It is converted by internal oxidation to morphinic acid (124).

MORPHINIC ACID (Morphinonic acid (207)) is prepared by heating morphine quinitrol in aqueous solution at 100°; the acid separates as the NITRATE, $C_{17}H_{19}O_6N \cdot HNO_3 + H_2O$; it decomp. slowly without melting. The HYDROCHLORIDE cryst. from water in colorless needles holding two molecules of crystal-water. The OXIME HYDROCHLORIDE is crystalline (124).

DIHYDROMORPHINIC ACID, TETRAHYDROMORPHINIC ACID, from ozonization of morphine derivatives, see page 199.

OZODIHYDROETHYLMORPHINE, is an oily base obtained from the action of ozone on dihydroethylmorphine (structure, see p. 187). The HYDRIODIDE, $C_{19}H_{25}O_3N \cdot HI$ cryst. from alcohol in needles decomp. 255 ° to 256°, $[\alpha]_D^{17} = +69.1°$ (water, C=2.508). The base hydrolyzes to dihydromorphinic acid (207). Electrolytic reduction gives 5-desoxydihydromorphinic acid (p. 199). Reduction of ozodihydroethylmorphine with palladium and hydrogen yields 5-DESOXYDIHYDROMORPHINIC ACID 3-ETHYL ESTER, noncrystalline, but giving a PICRATE decomp. 234° to 235°. The ethyl ester hydrolyzes to 5-desoxydihydromorphinic acid (207).

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PSEUDOMORPHINE

This base, which has also been called oxymorphine (1), oxydimorphine (2), dehydromorphine (3), or phormin (4), was first isolated in 1835 by Pelletier (5) (6) (7) in an investigation of the alkaloids from opium. It is formed by gentle oxidation of morphine, especially in alkaline solution; whether pseudomorphine occurs as such in opium or is first formed during the chemical processes involved in the separation of the opium alkaloids is still uncertain (4). It has been observed in oxidations of morphine with potassium permanganate (8), ferricyanide (2) (9), bromine (10), nitrous acid (1) (11), ammoniacal cupric solutions (12), or hydrogen peroxide with potassium cuprous cyanide (13) (14). Pseudomorphine is produced when ammoniacal solutions of morphine are allowed to stand in contact with the air (15) or even when solutions of morphine hydrochloride are sterilized in a sealed tube; a trace of acid or reducing agent hinders the oxidation in the last case (16) (17). Firbas reports pseudomorphine formation by the action of an oxidase present in gum arabic (18); an oxidizing ferment, morphinase, present in *Russula delica* Fr. also accomplishes the oxidation of morphine to pseudomorphine (19) (20). (*Cf.* Moureau (21).) Pseudomorphine was claimed by Marmé to be a product of the degradation of morphine in the body (22), although this has been questioned (23). The separation of the base from opium, from which it is obtained only in minute amounts (about 0.02%), is described by Hesse (24), its separation from morphine by Balls (25).

Bromomorphine (p. 146) which carries the bromine in the aromatic nucleus, is not oxidable to a pseudomorphine analog (26), nor are codeine, diacetylmorphine, or methylmorphimethine (27).

Oxidation of morphine methiodide with potassium ferricyanide gives pseudomorphine methiodide methohydroxide

$$\begin{matrix} C_{17}H_{18}O_3N\cdot CH_3I \\ | \\ C_{17}H_{18}O_3N\cdot CH_3OH \end{matrix}$$

which is converted to pseudomorphine dimethiodide by hydriodic acid (28).

Concerning the structure of pseudomorphine little is known with certainty. Polstorff (2) (29) assigned it a dimolecular structure, since by similar oxidation of morphine methiodide an ammonium base could be obtained which was capable of forming basic salts. Polstorff's view was confirmed by the molecular weight determinations of Bertrand and Meyer (30) (31) (32) and by the preparation of a basic pseudomorphine hydrochloride by Hesse (33).

Pseudomorphine forms a tetraacetyl derivative (33) (34), indicating that the molecule contains four hydroxyl groups. Only one of these behaves as a phenolic hydroxyl; a monomethyl ether can be obtained, which is insoluble in alkali, and contains three alcoholic hydroxyl groups (27). The two nitrogen atoms in pseudomorphine also show a marked difference in behavior—the dimethiodide of pseudomorphine loses one atom of iodine readily with alkali, while the second iodine is very resistant (27). (*Cf.* the basic methiodide obtained when morphine methiodide is oxidized to a pseudomorphine derivative (28).)

In analogy with the formation of dimolecular products through oxidation of the higher phenols or the naphthols, pseudomorphine is regarded as being formed by a carbon to carbon union of two molecules of morphine (27), with removal of two hydrogens by oxidation (35):

$$2C_{17}H_{19}O_3N+2KOH+2K_3Fe(CN)_6=\left|\begin{matrix}C_{17}H_{18}O_3N\\ C_{17}H_{18}O_3N\end{matrix}\right.+2H_2O+2K_4Fe(CN)_6$$

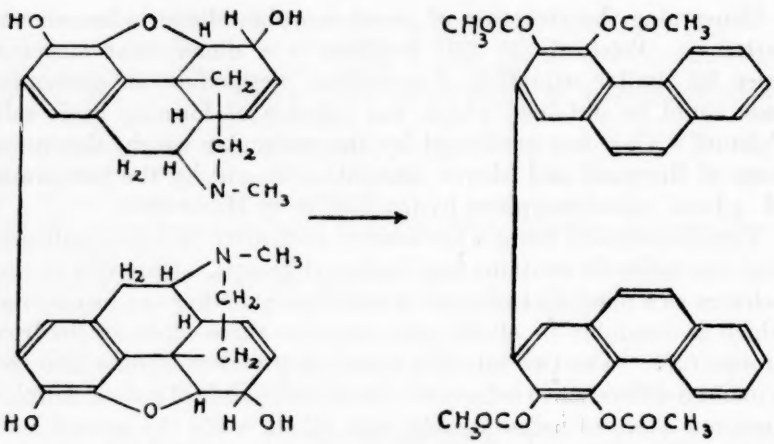
This does not explain the loss of the phenolic function by one hydroxyl group, nor the differences in properties exhibited by the two nitrogen atoms.

In further analogy with the naphthol ethers, methylated morphine derivatives, as codeine or methylmorphimethine, would not be expected to oxidize to pseudomorphine derivatives (27). Since bromomorphine does not undergo such an oxidation, the union of two molecules in the case of morphine is thought to take place through the carbon atoms occupied by bromine (C-1 or C-2) in bromomorphine.

The action of reducing agents, as sodium amalgam in alkaline solution, zinc or tin and hydrochloric acid, changes pseudomorphine, but does not convert it back to morphine (3). (*Cf.* also Balls (14).)*

By acetolysis of pseudomorphine methiodide methohydroxide, Goto and Kitasato (43) succeeded in degrading pseudomorphine to a dimorphol derivative, bis-(2,2′)-3,4-diacetylmorphol; these investigators regard pseudomorphine as 2,2′-dimorphine:

* See Appendix, p. 361.



Pseudomorphine Bis-(2,2′)-3,4-diacetylmorphol

Pseudomorphine gives with ferric chloride a dark indigo color; it frees iodine from iodic acid; with chlorine-water it gives a green color, becoming yellow-green to brown on addition of ammonia (36). The action of a large number of precipitants is given by van Itallie and Toorenburg (37). Marquis' reagent gives a red color, turned to green by a trace of potassium ferricyanide (38) (39). Fröhde's reagent gives an intense blue; ammonium selenite in concentrated sulphuric acid, violet (19).

Quantitative estimation of pseudomorphine as free base, sulphate, or silicotungstate is described by Balls (25). *Cf.* Marmé (22), Donath (23).

Descriptive Part (Pseudomorphine)

PSEUDOMORPHINE: $B=C_{34}H_{36}O_6N_2$, prepared by oxidation of morphine in alkaline solution with $K_3Fe(CN)_6$; finely powdered morphine suspended in water is treated with the calculated amount of normal potassium hydroxide, and a solution of potassium ferricyanide in the theoretical quantity added slowly. The yellow precipitate is filtered off, and dissolved in a slight excess of sodium hydroxide; carbon dioxide precipitates the base crystalline from this solution. It is purified by dissolving in hydrochloric acid, filtering, and again precipitating from alkaline solution. Yield, 84% (2) (27). The base is also purified by dissolving in strong ammonia, and removing the ammonia in vacuum (31) (33). Oxidation with hydrogen peroxide in the presence of potassium cuprous cyanide (13) at pH 6.5 gave maximum yields of 25% (14). Pseudomorphine separates as a colorless crystalline powder or crust, apparently rhombic plates, containing 3 molecules of hydrate water, from ammoniacal solution (2). It becomes anhydrous at 150°, and decomp. about 327°; $\alpha=-2.16°$ (0.2135 g. anhydrous base in 25 c. c. of normal HCl, l=22 cm.) (31). *Cf.* Hesse (40). The base is insoluble in cold water, alcohol, ether, chloroform, carbon disulphide, dil. sulphuric acid, or sodium carbonate; slightly soluble in ammonium hydroxide, especially hot, soluble in alkalies (24) (*cf.* Bertrand and Meyer (31)). It is insoluble in the liquid hydrocarbons, lower aliphatic ethers, esters, or alkyl halides; soluble in traces in hot butyl, amyl, or heptyl alcohol. Pyridine, aniline, guaiacol, cresols, and benzyl alcohol are the best solvents; it is slightly soluble in alcoholic ammonia (44). The isoelectric point for pseudomorphine lies at about pH 8, with a rather wide range, so that it may be separated from morphine by precipitation in slightly acid solutions (14). —HYDROCHLORIDE, $B\cdot(HCl)_2+xH_2O$; crystal-water variable, depending upon conditions: $+2H_2O$, Hesse (24), $+4H_2O$, $+6H_2O$,

$+8H_2O$, Polstorff (41), Hesse (33). It decomposes at about 350°; 1.4 parts dissolve in 100 parts of water; $[\alpha]_D = -107.7°$ (31). (*Cf.* Donath (3) for the anhydrous salt, $[\alpha]_D^{24} = -103.13°$ [water, p=0.9509]; Hesse (40).) A BASIC HYDROCHLORIDE, $B{\cdot}HCl+6H_2O$ is known, which precipitates when sodium chloride is added to a hot neutral solution of pseudomorphine in acetic acid; from cold solution, $B{\cdot}HCl+8H_2O$ separates; sparingly soluble in hot water, insol. in cold water or alcohol. It gives the same PLATINICHLORIDE as the neutral salt: $B{\cdot}(HCl)_2{\cdot}PtCl_4+8H_2O$ (33). —MERCURICHLORIDE, colorless prisms (24).

—HYDRIODIDE: $B{\cdot}(HI)_2+2H_2O$, pale yellow efflorescent crystals, soluble in 793 parts of water at 18° (24) (33).

—SULPHATE: $B{\cdot}H_2SO_4+6H_2O$, efflorescent, crystallizes from boiling water with $8H_2O$, in concentric-grouped leaflets (2) (33) soluble in 422 parts of water at 20° (1:500 (19)), insol. in alcohol or ether (24). The salt may be used to separate pseudomorphine from morphine (25).

—HYDROBROMIDE: White, sparingly sol. prisms (42).

—DICHROMATE: $B{\cdot}H_2Cr_2O_7+6H_2O$, small yellow-brown prisms, soluble in 1090 parts water at 18° (33) (42).

—OXALATE: $B{\cdot}H_2C_2O_4+8H_2O$, white cryst. precip. soluble in 1,940 parts of water at 20° (24) (33).

—BITARTRATE: $B{\cdot}(C_4H_6O_6)_2+6H_2O$, concentric-grouped needles, diff. sol. in water (24) (33).

PSEUDOMORPHINE METHIODIDE METHOHYDROXIDE: $B{\cdot}(CH_3I)\ (CH_3OH)+5H_2O$, prep. by oxidation of morphine methiodide; small colorless plates from hot water (28), m. p. 294° (decomp.), yield 70% to 80% (43). With hydriodic acid it gives the DIMETHIODIDE. The methiodide methohydroxide was degraded by boiling with acetic anhydride and sodium acetate, freeing from halogen with silver acetate, and heating the filtrate 24 hours at 180°; the product, bis-(2,2′)-3,4-diacetylmorphol cryst. from glacial acetic acid in prisms of m. p. 255° (43). PSEUDOMORPHINE DIMETHIODIDE, $B{\cdot}(CH_3I)_2+4H_2O$, pale yellow cryst. from water (28). PSEUDOMORPHINE METHOSULPHATE, $B{\cdot}(CH_3)_2SO_4+4H_2O$, yellow leaflets, sol. in hot water, sparingly sol. in cold water (28). PSEUDOMORPHINE DIMETHOHYDROXIDE, $B{\cdot}(CH_3OH)_2+7H_2O$, precip. from hot water by alcohol as a poorly cryst. powder (28).

TETRAACETYLPSEUDOMORPHINE (33): $C_{34}H_{32}(OC_2H_3)_4O_6N_2+8H_2O$, (Danckwortt (34), $+5H_2O$), prep. by heating pseudomorphine with acetic anhydride for 2 hours at 120°; flat concentric-grouped prisms from ether, sintering about 250°, melting completely at 276°. Fairly soluble in ether or chloroform, very sol. in alcohol, with strongly basic reaction. The HYDROCHLORIDE is crystalline and readily sol. in water (*cf.* Danckwortt (34), $C_{34}H_{32}Ac_4O_6N_2{\cdot}2HCl+4H_2O$, diff. sol. in water), —PLATINICHLORIDE cryst. with $6H_2O$.

PSEUDOMORPHINE METHYL ETHER (27): $C_{35}H_{38}O_6N_2+7H_2O$, colorless needles, blackening at 257°, melting above 280°; insol. in hot water, alcohol, alkali, ether, or chloroform; it is precipitated cryst. from its salts by alkali. —HYDROCHLORIDE, $C_{35}H_{38}O_6N_2{\cdot}2HCl+4H_2O$, colorless wedge-shaped leaflets, sol. in cold water. The PLATINICHLORIDE consists of anhydrous, yellow flocks. The SULPHATE, efflorescent white needles, contains variable crystal-water, and is much more soluble than pseudomorphine sulphate. The METHIODIDE, $C_{35}H_{38}O_6N_2{\cdot}2CH_3I+4H_2O$, forms at 110° under pressure as concentric-grouped pointed prisms, sol. in hot water. With ammonia it gives a cryst. precip. of the basic METHIODIDE, $C_{35}H_{38}O_6N_2(CH_3I)\ (CH_3OH)+6H_2O$, leaflets from hot water.

DIBENZOYLPSEUDOMORPHINE, and TRIBENZOYLPSEUDOMORPHINE are not crystalline (27). TRIBENZOYLPSEUDOMORPHINE METHYL ETHER is amorphous, but gives a cryst. Hydrochloride; the Triacetyl derivative likewise was isolated and analyzed as the hydrochloride and platinichloride (27).

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CODEINE

Codeine, $C_{18}H_{21}O_3N$, the methyl ether of morphine, was first isolated in 1832 by Robiquet (1) (2), who found it as an impurity accompanying morphine which had been extracted from opium by the Gregory process. Analyses by Regnault (3) (4), Liebig (5), and others (6) (7) (8) resulted in the proposal of various empirical formulas; Gerhardt

(9) (10) (1842) first obtained values corresponding to $C_{18}H_{21}O_3N + H_2O$. Gerhardt's analyses were confirmed by Anderson (11). Wright (12) believed that this formula should be doubled; his view has not been accepted.

Codeine is found in opium in far smaller amounts than morphine, usually between the limits 0.2% to 0.8% (13). It has not been reported as occurring in any plant other than the poppy. Codeine is the second alkaloid to appear in the young plant, being first detectable about 30 days after the seed has sprouted; poppy seeds contain no codeine (14). Its character as the methyl ether of morphine was first established by Grimaux (15) in 1881, although speculations to this effect (16) (17) had appeared previous to this time. Since the development of practicable alkylation methods, it has been obtained largely from the more abundant morphine by methylation (see below).

Of the numerous separation procedures, those based on the Gregory (18) method have probably found the most application. The concentrated aqueous extract from finely powdered opium is treated with strong calcium chloride solution, which removes as calcium salts the meconic acid, lactic acid, and sulphuric acid. From the mother liquor the so-called Gregory-salt, a mixture of the hydrochlorides of morphine and codeine, crystallizes. Ammonia precipitates the morphine from a solution of the purified Gregory-salt, while the codeine remains in solution from which it may be separated by extracting with benzene or by concentrating to the point where a mixture of ammonium chloride and codeine hydrochloride crystallizes.

Other methods which have been proposed for the separation of codeine are those of Merck (19) (20), Mohr (21), Hesse (22) (23), and Plugge (24) (25). A recent paper by Kanewskaja (26) reviews these procedures and describes a newly developed process which permits the isolation of 87% of the codeine present in opium.

The preparation of codeine by methylation of morphine was accomplished independently by Grimaux (15) (27) (1881) and Hesse (28) by the action of methyl iodide on morphine in the presence of alkali. Since the morphine and codeine are converted in large part to the methiodides, the yield of codeine base is very small. A number of more advantageous methods have been developed in factory practice, and are reported in the patent literature as follows:

Methylation of morphine or morphine alkali salts with salts of methyl sulphuric acid, A. Knoll (29) (30).

Methylation in the presence of sodium methylate or sodium ethylate using dimethyl sulphate (31), trimethyl phosphate (32), or methyl nitrate (33), E. Merck.

Methylation of morphine alkali salts with dimethyl sulphite, Gerber (34).

Methylation of morphine-N-oxide with dimethyl sulphate and alkali, and reduction of the resulting codeine-N-oxide to codeine, E. Merck (35).

The use of diazomethane was covered in 1896 by patents of Farbenfabr. vorm. Friedr. Bayer & Co. (36) (37) (38), which included modifications using nitrosomonomethylurea (39), p-toluenesulphonitrosomethylamide or nitrosomethylbenzamide (40).

Methylation with esters of sulphonic acids, as methyl benzene sulphonate, E. Merck (41).

The most advantageous methylation process has proved to be that using phenyltrimethylammonium hydroxide (Boehringer Sohn (42)) as methylating agent:

$$\underset{\text{Morphine}}{HO(C_{17}H_{17}ON)OH} + C_6H_5N(CH_3)_3OH \longrightarrow \underset{\text{Codeine}}{CH_3O(C_{17}H_{17}ON)OH} + C_6H_5N(CH_3)_2 + H_2O$$

There is no loss of morphine or codeine through formation of quaternary N-alkyl compounds, and the dimethylaniline formed during the reaction is readily removed by steam distillation. A modification of this method, due to Rodionov (43), may be operated conveniently and economically on a laboratory scale. (See descriptive section, p. 188.)*

Codeine crystallizes from dry ether or benzene in small anhydrous prisms of m. p. 155°. From water or dilute alcohol large clear rhombic prisms (44) holding one molecule of crystal-water are obtained; the hydrated base sometimes shows a melting point below that of the anhydrous (6), depending upon the mode of heating. Transparent rhombic octahedra separate from moist ether. Deane and Brady (45) describe the crystals from alcohol or water as octahedra running to four-sided prisms (crystal drawings given). The base crystallizes from carbon disulphide in anhydrous rhombohedra (46). Crystal measurements have been published by Keferstein (47), Senarmont (48), Arzruni (46), Wherry and Yanovsky (49), and Heydrich (50). Hydrated codeine crystals effloresce somewhat on exposure to air, and lose their crystal-water completely at 100°. The hydrated base also becomes anhydrous in boiling water, melting to an oily liquid.

Gaubert (51) states that codeine crystallized above 60° forms rhombic hemihedral crystals, the stable (α) form. At lower temperatures it exists in four kinds of spherulites, viz, a β-form at ordinary temperatures, a γ-form at about 40° and two other spherulite forms between 45° and 60°. These modifications differ in their power to rotate the plane of polarization. Kremann and Schniderschitz (52) could find no evidence in the cooling curve of codeine for the existence of Gaubert's spherulites.

Codeine is sparingly soluble in water; it in much more soluble than morphine in most organic solvents. One gram of codeine dissolves in 120 g. of water, 1.6 g. of alcohol, 0.75 g. chloroform or 13 g. of ether, at 25°; in 0.96 g. of alcohol at 60° (53). Other values for the solubility are given in the accompanying table.

* See Appendix, p.362.

Table of solubilities

[Grams of codeine in 100 g. of solvent]

Solvent	Solubility	Observer
Water	0.9 (20°), 1.1 (40°), 3.2 (100°)	Rakshit (54).
Do	1.28 (15°), 3.77 (43°), 5.88 (100°)	Robiquet (2).
Do	1.17 (cold), 5.9 (hot)	Knoll (30).
Do	0.85 (15°)	Tambach and Henke (55).
Ammonia 10% w/v	0.9 (20°), 1.5 (40°), 3.2 (80°)	Rakshit (54).
Alcohol 90%	27.0 (20°), 61.0 (40°), 89.5 (90°)	Do. (54).
Amyl alcohol	15.68 (temperature not given)	Kubly (56).
Ether	3.4 (20°)	Rakshit (54).
Acetone	20.4 (20°), 26.4 (40°), 36.3 (50°)	Do. (54).
Chloroform	22.8 (20°), 35.4 (40°), 47.4 (50°)	Do. (54).
Carbon tetrachloride	1.328 (17°)	Schindelmeiser (57).
Benzene	8.3 (20°), 17.6 (40°), 72.5 (80°)	Rakshit (54).
Do	9.6 (temperature not given)	Kubly (56).
Anisole	7.8 (9°), 15.28 (16°), 164.0 (100°)	Fouquet (58).

Codeine which has been crystallized once from anisole becomes more soluble in this medium, dissolving to the extent of 10.7 g. per 100 at 0° (58).

For the density of codeine crystals (hydrate), Schröder (59) found the values 1.323 and 1.311; Wherry (49) gives the specific gravity of anhydrous or hydrated crystals as 1.31. The refractive indices (Kley (60)) are 1.66 and 1.56; Wherry and Yanovsky (49) give for anhydrous codeine crystals n_D: $\alpha=1.62$, $\beta=1.63$, $\gamma=1.65$; for the monohydrate, n_D: $\alpha=1.54$, $\beta=1.64$, $\gamma=1.69$. (*Cf.* Wright (61).) In a cathode-light vacuum codeine boils and distills at 179° (62). Kempf (63) sublimed codeine at 1.5 mm. pressure at 140° to 145°; the sublimed product showed the melting point 157°. Eder (64) accomplished the sublimation at 10 mm., 100° to 130°. Microsublimation methods are described by Heiduschka (65).

Codeine solutions are levorotatory. Hesse (66) found the values $[\alpha]_D^{15}=-135.91°$ (97% alcohol, p=2) and $[\alpha]_D^{15}=137.75°$ (80% alcohol, p=2), the degree of rotation being practically independent of the concentration. In chloroform, $[\alpha]_D^{15}=-111.5°$ (p=2) (66). The earlier determination of Bouchardat and Boudet (67) gave $[\alpha]=-118.2°$ (alcohol); in a later determination Grimaux (68) found $[\alpha]_D=-130.34°$ (codeine prepared from morphine) and $[\alpha]_D=-133.18°$ (C=1.43) for natural codeine. Tykociner (69) reported values for numerous codeine salts, all in the neighborhood $[\alpha]_D=-134°$.

The absorption spectrum of codeine solutions was studied by Hartley (70), and Kitasato (71), that in the ultra-violet by Brustier (72) and Steiner (73). Gompel and Henri (74) compared the ultra-violet absorption spectrum with that of other phenanthrene alkaloids and of phenanthrene itself.

Codeine is a strong monoacid base; in aqueous solution it turns litmus blue, colors phenolphthalein and turns red helianthin yellow (75). It is precipitated (often in crystalline form) from solutions of its salts only incompletely by ammonia. Electrometric titration of

codeine hydrochloride shows the neutral point to lie at pH 4.93 (76) (77), whence methyl red is recommended as indicator for codeine titrations. See also Kolthoff (78), Müller (79), Kebler (80), Kippenberger (81), Masucci and Moffat (82).

Thermochemical studies on codeine were carried out by Leroy (75) (83). The heat of combustion at constant volume is 2325.8 Cal., at constant pressure 2327.7 Cal.; heats of hydration, solution, and neutralization were also measured.

The more important color and precipitation tests which have been proposed for codeine are outlined in the following table.

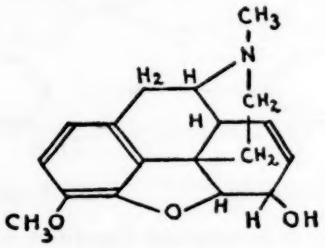
Codeine precipitation and color reactions

Reagent	Reaction	Observer
Conc. H_2SO_4 containing $FeCl_3$	Blue, becoming dirty-green at about 150°. *Cf.* ref. 53.	Hesse (84) (85) (86).
Conc. H_2SO_4 and sugar	Base moistened with moderately conc. sol. of sugar, and a drop of H_2SO_4 added: purple-red color, changing after ½ hour.	Schneider (87).
Tattersall test: Sodium arsenate and conc. H_2SO_4.	Green or blue; dilute and add NaOH, yellow.	Tattersall (88), Vitali (89).
H_2SO_4 containing HNO_3	Pale green, becoming violet-green	Couerbe (6).
HNO^3, followed by alcoholic KOH.	Brick-red	Vitali (90).
Boil with PbO_2 and acetic acid; filter and add H_2SO_4.	Filtrate pale yellow, becomes intense blue-violet with H_2SO_4.	Deér (91).
Silicotungstic acid	Buff ppt. slightly sol. in alcohol or dilute acids.	Bertrand (92), North and Beal (93), Heiduschka and Wolf (94).
Phosphotungstic acid	Precipitate	Heiduschka and Wolf (94).
Vanillin, or piperonal, with a few drops of 0.5 *N* H_2SO_4.	Evap. dry on steam bath: blue-violet	V. Itallie and Steenhauer (95) (96).
Ammonium uranate $+H_2SO_4$	Blue color	Brociner (97).
Uranium salts, solarized	Intense blue. Unsolarized solutions give no color.	Aloy (98) (99).
Ammonium selenite in conc. H_2SO_4.	Brilliant green; given also by morphine	Lafon (100), da Silva (101).
Marquis' Reagent: 3cc. conc. H_2SO_4+3 drops 30% HCHO sol.	Red-violet, becoming blue-violet	Kobert (102), Linke (103) Elias (104).
Magnol (basic magnesium hypochlorite).	5 mg. alkaloid in 3 cc. of acetic acid cont. 2% Magnol, layered onto 3 cc. conc. H_2SO_4: pale green stripe over lilac layer over green-brown (Resoflavin color)	David (105).
Sodium hypochlorite solution +conc. H_2SO_4.	Sky-blue	Raby (106).
Antimony trichloride	Pale green color	Smith (107).
Zinc chloriodide	Precip. of hairlike light brown crystals	Tunmann (108).
Iodine chloride	Precipitate	Dittmar (109).
Benzidine	0.02 g. base dissolved in 2 cc. conc. H_2SO_4 with 0.01 g. benzidine: yellow, becoming brown, then dark green; added to water, gives a violet solution, from which $CHCl_3$ extracts color. Test given also by morphine, dionin, heroin and apomorphine.	Ekkert (110).
Chlorine-water	No color	Marmé (111).
Potassium iodate or iodic acid	Not reduced. *Cf.* Rosenthaler, (112) formation of clumps of crystals.	Do. (111).
Pellagri-Vulpius reaction		Ekkert (113).

Wagenaar (114) describes numerous microchemical precipitation reactions for codeine; Kerbosch (14) gives the action of a large number of precipitants. Tunmann (115) describes the use of codeine triiodide as a means of identification.

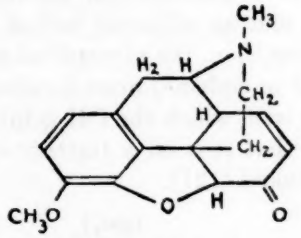
The estimation of codeine in the presence of morphine and in opium preparations is discussed by Taylor (116); see also Rakshit (54).

The structural problem of codeine is intimately associated with that of morphine and of thebaine, and will therefore be considered in a separate section (p. 336). For convenience in depicting the reactions of codeine, the Gulland and Robinson formula of 1925 (117) will be used in the following discussion.



Codeine

Codeine is far more stable toward oxidizing agents than is morphine; it is unaffected in alkaline solution by oxygen, and does not give the reduction reactions which characterize morphine. Attempts to oxidize codeine with mercuric acetate resulted only in complex products containing mercury (118). It is oxidized by potassium permanganate in acetone, or chromic acid in dilute sulphuric acid at 50°, to the ketone codeinone (119) (p. 247).

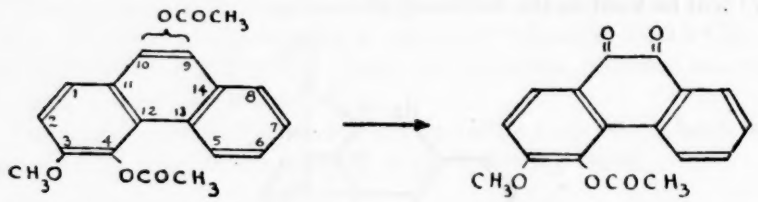


Codeinone

Very dilute permanganate (120) effects addition of two hydroxyl groups to the hydroaromatic double bond (p. 186).

The action of cold chromic-sulphuric acid mixture converts codeine into 9-hydroxycodeine, $C_{18}H_{21}O_4N$ (119). Two alcoholic hydroxyl groups are present in this base; it has no phenolic properties, and forms a diacetyl derivative. The methine base obtained in the first step of the Hofmann degradation of hydroxycodeine methiodide, on heating with acetic anhydride, is split into ethanoldimethylamine and a methoxydiacetoxyphenanthrene (121). In this compound the new hydroxyl of hydroxycodeine must still be present (as acetoxy group), for under similar conditions methylmorphimethine (from codeine) yields methoxyacetoxyphenanthrene (see p. 270). Oxidation of the above-mentioned trihydroxyphenanthrene derivative gave the known (122) methylacetylmorpholquinone, whose structure as 3-methoxy-4-

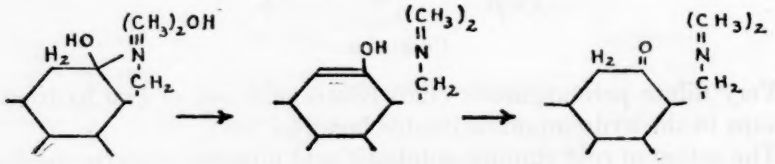
acetoxyphenanthrene-9,10-quinone was certain from its synthesis (123). One acetyl group disappeared in quinone formation, hence it (and the hydroxyl of hydroxycodeine which it represents) must have been located on C-9 or C-10 (124).



Methoxydiacetoxyphenanthrene Methylacetylmorpholquinone

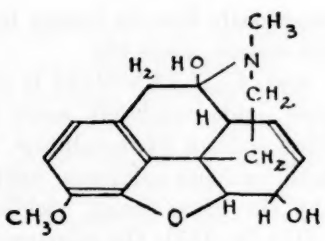
Since the hydroxyl group in question functions as an alcoholic group in hydroxycodeine, it follows that the 9, 10-positions in this base, and in codeine, must be hydrogenated (124).

Further information concerning the structure of hydroxycodeine and codeine was obtained from a study of the ketodihydromethylmorphimethine resulting from the action of hot alkali on hydroxycodeine methiodide. Ketodihydromethylmorphimethine (at first erroneously named hydroxymethylmorphimethine (121)) proved to be a ketone (125) (oxime, semicarbazone), from which it follows that a double linkage must have been formed between the carbon atom carrying the hydroxyl and an adjacent carbon atom as a result of opening the nitrogen ring, i. e., the nitrogen of the ethanamine chain in hydroxycodeine (and in codeine) must be attached to C-9 or C-10 (125) (126). The ease with which the OH is introduced into codeine by oxidation indicates that it is on a tertiary carbon atom, that to which the nitrogen is linked (121).



This transition of a hydroxyl to a keto group during degradation has its parallel in the formation of methylcinchotoxin from cinchonine methiodide, or of narceine from narcotine methiodide (p. 82).

Linkage of the ethanamine nitrogen to C-9 in preference to C-10 has been generally accepted as most probable; no definite proof of this exists. 9-Hydroxycodeine may be represented:

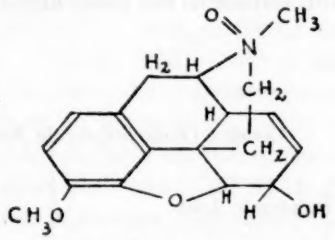


9-Hydroxycodeine

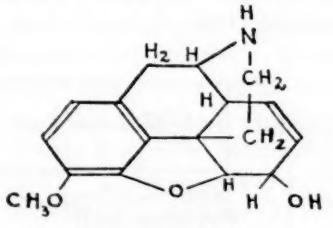
9-Hydroxycodeine does not form a nitrocodeic acid like codeine and pseudocodeine (127).

Other hydroxycodeines, isomeric with 9-hydroxycodeine have been described. The 2-hydroxycodeine of Freund (128) and Wieland (129) was prepared from nitrocodeine through the amino and diazonium derivatives (p. 183). 7- or 14-hydroxycodeine (117) (130) results from reduction of hydroxycodeinone (131) (132) and is described on page 256. The investigations of Dobbie and Lauder (133) indicated that neopine might be a hydroxycodeine; later work has shown it to be an isomer of codeine (134) (p. 205).

Hydrogen peroxide acts on codeine to form codeine-N-oxide (135), in which the codeine molecule is essentially intact; the oxide is reduced back to codeine by such agents as sulphur dioxide or sodium hydrosulphite. Codeine oxide is converted by potassium chromate into norcodeine (N-demethylocodeine, p. 184) with loss of formaldehyde (136).

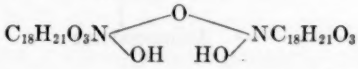


Codeine Oxide

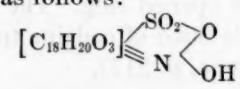


Norcodeine

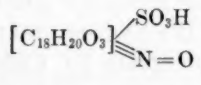
Mossler and Tschebull (137) describe a dimolecular codeine oxide hydrate, to which they assign the formula



Hydrochloric acid splits it to the hydrochloride of a codeine oxide hydrate. When ordinary codeine oxide is treated with acetic anhydride-sulphuric acid mixture, two isomeric codeine-N-oxide sulphonic acids can be obtained (128); the isomerism was represented by Freund as follows:



α-Codeine Oxide Sulphonic Acid



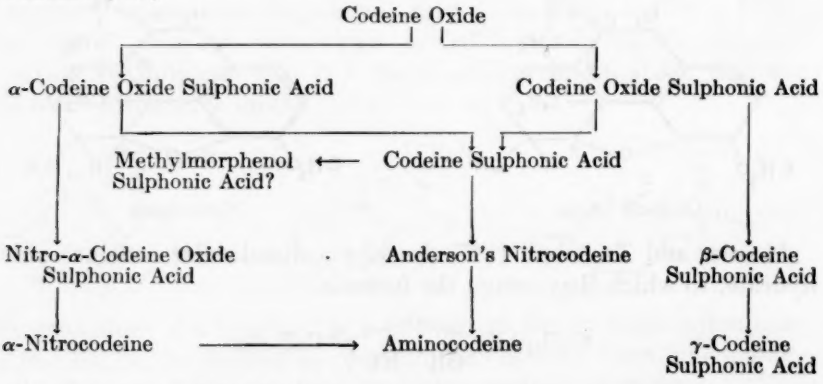
Codeine Oxide Sulphonic Acid

The α-form is converted easily into its isomer by the action of alkali or acid; see descriptive section, page 192.

Codeine sulphonic acid, $C_{18}H_{20}O_3N \cdot SO_3H$ is obtained when either of the isomeric codeine oxide sulphonic acids is reduced with sulphurous acid or alkaline sodium hydrosulphite. On treatment with concentrated nitric acid, codeine sulphonic acid suffers replacement of the SO_3H group by the nitro group, yielding the known nitrocodeine of Anderson (11) (p. 183); the sulphonic acid group is therefore believed to occupy the same position in the molecule as does the nitro group in nitrocodeine. Codeine sulphonic acid has been degraded to a nitrogen-free product, apparently a morphenol-sulphonic acid derivative, $C_{14}H_5O(OCH_3)_2(SO_3K)$ (128).

When codeine oxide sulphonic acid is treated with cold concentrated sulphuric acid, a compound is obtained which appears to be an isomer of codeine sulphonic acid, and which was therefore named β-codeine sulphonic acid. On digestion with sulphurous acid, it is converted to a new compound of the same empirical formula, known as γ-codeine sulphonic acid (128). No hypothesis concerning the isomerism has been put forward.

α-Codeine oxide sulphonic acid yields with cold nitric acid nitro-α-codeine oxide sulphonic acid; this substance reduces with sulphurous acid, losing the amine-oxygen and the SO_3H-group, to a new nitro-derivative, α-nitrocodeine. α-Nitrocodeine (m. p. 197°) and the nitrocodeine (m. p. 217°) of Anderson both reduce to the same aminocodeine (128).



Ozone reacts slowly with codeine to give an aldehyde, codinal (isolated as the phenylhydrazone), which is apparently identical with the product obtained from the ozonolysis of morphine (138). This indicates a rupture of the aromatic nucleus and loss of two carbon atoms and the methoxyl group of the opened ring. The remarkable inactivity of the hydroaromatic double bond of codeine toward ozone is difficult to explain (*cf.* Chlorocodizone, p. 212).

Concentrated sulphuric acid converts codeine into an amorphous product (11) of unknown nature, which has been named apocodeine (139) (140). The apocodeine which is formed by heating codeine with zinc chloride (141) (142) (143) consists of complex amorphous bases together with some chlorocodide, apomorphine, and unchanged codeine. An amorphous base resulting from treatment of chlorocodide or bromocodide with alkaline reagents (144) (145) (146) was also designated as apocodeine; it is probably a mixture of apomorphine with other substances of unknown nature (145). When codeine is melted with oxalic acid, pseudocodeine (the dicodeine of Beckett and Wright (147)) and pseudoapocodeine are formed (148). Better yields of pseudoapocodeine are obtained from the oxalic acid melt of pseudocodeine, which is therefore believed to represent an intermediate step in the codeine transformation. Pseudoapocodeine is related to apomorphine as codeine to morphine, i. e., it is the 3-methyl ether of apomorphine (149).*

By methylation of apomorphine a monomethyl ether is obtained (150), which is identical with pseudoapocodeine (149). Further methylation results in apomorphine dimethyl ether (149), whose synthesis is described on page 264.

According to Fulton (151) the action of concentrated sulphuric acid on codeine at 40° gives a solution which sets to a jellylike mass of crystals on dilution; no conjecture as to the nature of this product has been made.

Hot concentrated hydrochloric or hydrobromic acid converts codeine partly to β-chlorocodide (152) or bromocodide, respectively (see p. 212), and partly to complicated amorphous products, named by Wright (153) (154) (155) as tetracodeine derivatives. At the same time, demethylation and rearrangement into apomorphine take place to some extent (16) (156) (157). With hydriodic acid, or hydriodic acid and phosphorous, methyl iodide is evolved, and amorphous basic products result (12) (155) (158). These so-called polymers of codeine, dicodeine, tricodeine, and tetracodeine, were studied in a long series of papers by Beckett and Wright (143) (147) (159) (160) without noteworthy results. Knorr and Roth (148) state that dicodeine is probably identical with pseudocodeine.

Codeine is nitrated by strong nitric acid, yielding a nitrocodeine (11) (161) of m. p. 221° (127), in which the nitro group is believed to occupy the 2-position. Phosphorous pentachloride replaces the alcoholic hydroxyl of nitrocodeine by chlorine (162). The nitro group of nitrocodeine may be reduced in various ways (see p. 193) to give 2-aminocodeine, and the latter converted through the diazonium compound into 2-hydroxycodeine (128) (129), an alkali-soluble phenolic substance. By oxidation with concentrated nitric acid, 2-nitrocodeine is transformed to a dibasic amino acid, $C_{16}H_{18}O_9N_2$, nitrocodeic acid, containing two carbon atoms less than nitrocodeine. The hydro-

*See Appendix, p. 362.

aromatic ring III is believed to have been attacked (127). An isomer of 2-nitrocodeine, named α-nitrocodeine (m. p. 197°) was obtained by Freund and Speyer (128) (163) when α-codeine oxide sulphonic acid was nitrated and then reduced. α-Nitrocodeine yielded on reduction the same aminocodeine as is obtained from nitrocodeine.

The action of halogens on codeine was first studied extensively by Anderson (11). Chlorine or chlorine-water gives colored tarry products; chlorine generated by treatment of codeine hydrochloride with potassium chlorate or hydrogen peroxide (164) gives a well crystallized chlorocodeine in which the halogen is assumed to be on C-1 or C-2. The alcoholic hydroxyl group of chlorocodeine reacts with phosphorous pentachloride, giving chlorochlorocodide or dichlorocodeine (162). A second dichlorocodeine is known, from treatment of codeine with excess of phosphorous pentachloride (162) (p. 194). Bromine-water acts directly on codeine (11) (162) to give the same bromocodeine as is formed by oxidation of codeine hydrobromide with hydrogen peroxide (164). It yields with phosphorous pentachloride a bromochlorocodide (162). Bromocodeine (bromine in the aromatic nucleus) has been degraded to a bromomethylmorphimethine, which is known in two forms, analogous to α-and β-methylmorphimethine (165) (p. 274). Free iodine forms with codeine highly colored superiodides (166) (167). Iodine chloride gives a yellow crystalline diiodocodeine, which seems to be quite unstable and loses iodine easily (109) (168).

Cyanogen reacts with codeine to form the crystalline, somewhat unstable dicyanocodeine (11).

Codeine is acted upon by hydrogen sulphide in the presence of oxygen, but the nature of the products has not been determined (169).

A brownish-yellow sodium compound, or a red crystalline potassium compound is obtained when anhydrous codeine is refluxed in benzene with sodium or potassium. Analysis indicates that one hydrogen atom of codeine has been replaced by metal (170).

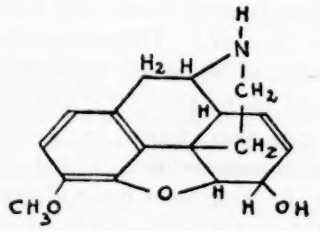
According to Vongerichten and Hübner (171) codeine can not be reduced with sodium and alcohol, or zinc and acetic acid; Knorr (172) states that reduction with sodium and alcohol or treatment with sodium ethylate converts codeine into high-melting, alkali-soluble bases; they are believed to be dimolecular in nature.

Codeine is regained unchanged from treatment with organomagnesium halides (173); at temperatures up to 150° it is but slightly affected by methyl magnesium iodide in isoamyl ether; at 170° decomposition takes place (174).

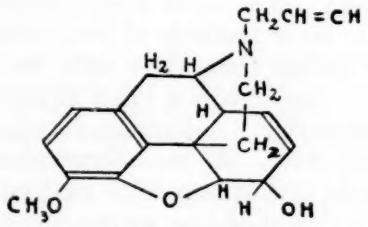
Codeine and p-nitrosodimethylaniline condense in alcohol solution to codeine-violet, an amorphous bronze-glistening substance, which dyes silk and wool directly (175).

Demethylation of codeine on nitrogen has been accomplished not only in the usual way with cyanogen bromide (176) (177), but also by treatment with nitrous acid and decomposition of the resulting N-nitrosonorcodeine (178), by the action of azodicarboxylic ester (179), and from codeine-N-oxide with potassium chromate (136). N-demethylocodeine, norcodeine, reacts with alkyl halides at 100°, and it has thus been possible to synthesize a large number of homologs of

codeine (see p. 196) carrying various alkyl groups on nitrogen. These derivatives are of great interest pharmacologically; N-allylnorcodeine in particular is said to have an action opposite to that of morphine (262). Norcodeine hydrogenates catalytically to the same dihydronorcodeine (p. 197) as is obtained from dihydrocodeine with cyanogen bromide.*

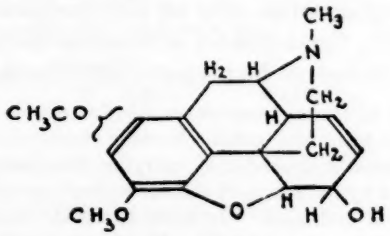


Norcodeine



N-Allylnorcodeine

By esterification of the alcoholic hydroxyl group of codeine, a large number of esters (p. 191) has been prepared. When acetic anhydride-sulphuric acid mixture is used as an acetylating agent, not only is the hydroxyl group esterified, but an acetyl group is apparently introduced into the nucleus (acetoacetylcodeine) (180) (181). This acetyl group is believed to occupy the same position (on C-1 or C-2) as the halogens or the nitro group in the halogenocodeines or in nitrocodeine (181), since acetocodeine, obtained by hydrolysis of the ester group in acetoacetylcodeine can not be nitrated; the position usually entered by the nitro group seems to be already filled by the acetyl group.



Acetocodeine

The hydroxyl group of codeine may be methylated, most conveniently through codeine-N-oxide, yielding codeine methyl ether (morphine dimethyl ether) (182). The Emde degradation of codeine methyl ether methochloride led to dimethylmorphimethine (183), taking in this case the same course as the Hofmann degradation (184) (p. 274).

When codeine is treated with phosphorous pentachloride (162) or thionyl chloride (129), the alcoholic hydroxyl is replaced by chlorine

*See Appendix, p. 362.

with formation of α-chlorocodide. This substance is easily converted to an isomer, β-chlorocodide (152) (185). The reactions and transformations of the chlorocodides are of such complexity and importance, that they are considered in a separate section (p. 209).

The unsaturated linkage in the hydroaromatic ring (III) of codeine is reduced readily by hydrogen in the presence of a catalyst, as platinum or palladium (186) (187). The same dihydrocodeine ("Paracodin") is obtained when dihydromorphine is methylated (35) (188). (For other methods of preparation, see p. 197.) Dihydrocodeine crystallizes from water with two molecules of water of crystallization; this dihydrate exists in two forms, of m. p. 55° (63°), and 88°, respectively. Anhydrous dihydrocodeine is also known, m. p. 112° (189) (190). All three forms give the same methiodide. The degradation of dihydrocodeine methiodide by the Hofmann method (191) is discussed in the section devoted to the methylmorphimethines (p. 271).

Dihydrocodeine is far more stable than codeine; it distills undecomposed in vacuum, and may be demethylated to dihydromorphine with hydriodic acid (189). It is recovered unchanged from vigorous treatment with chromic-sulphuric acid (191).

Many of the transformations known for codeine have been carried out on dihydrocodeine. It is nitrated by concentrated nitric acid (191); the same nitrodihydrocodeine results from the nitration of dihydrocodeine sulphonic acid (192). The latter substance, which may be prepared in several ways (p. 198), exists in two forms, like the codeine sulphonic acids; nitration of the so-called α-dihydrocodeine sulphonic acid yields a second (α-)nitrodihydrocodeine (192).

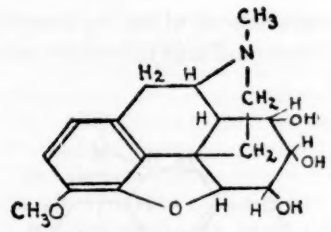
Phosphorous pentachloride acts on dihydrocodeine to form chlorodihydrocodide (191), the chemistry of which is discussed under chlorocodide (p. 214). It can not be prepared by reduction of chlorocodide.

The action of 30% hydrogen peroxide on dihydrocodeine gives dihydrocodeine-N-oxide (192), which resembles codeine-N-oxide chemically.

Chloro- and bromo-dihydrocodeine, carrying the halogen in the aromatic nucleus, are prepared by reduction of the corresponding chlorocodeine or bromocodeine with catalytic hydrogen. On more energetic reduction the bromine is reduced out of bromodihydrocodeine, to give dihydrocodeine (164).

Dihydrocodeine methyl ether (dihydromorphine dimethyl ether), obtained by catalytic reduction of codeine methyl ether (182) is identical with tetrahydrothebaine (130). Attempts to methylate dihydrocodeine to tetrahydrothebaine failed (130).

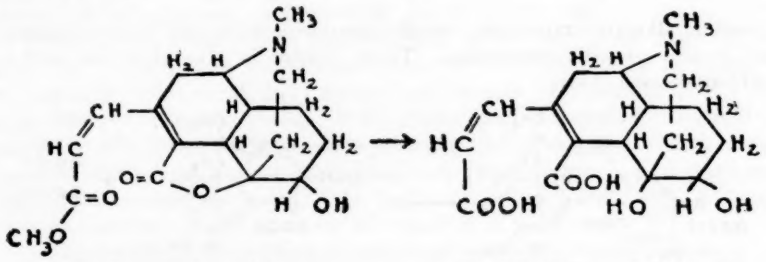
A dihydroxy derivative of dihydrocodeine was prepared by Cahn and Robinson (120) by the action of 1% potassium permanganate solution on codeine. It is believed to have the following structure:



Dihydroxydihydrocodeine

Nordihydrocodeine may be prepared by N-demethylation of dihydrocodeine with cyanogen bromide, or by catalytic hydrogenation of norcodeine (Von Braun (193)). As in the case of norcodeine, it has opened the way to the preparation of N-substituted dihydrocodeine derivatives. Nitrous acid acts on dihydrocodeine to form N-nitrosonordihydrocodeine (178).

By treatment of dihydrocodeine in formic acid solution with ozone, Speyer and Popp (194) obtained ozodihydrocodeine, which apparently results from scission of the 3, 4-double linkage of the aromatic nucleus of dihydrocodeine. Ozodihydrocodeine contains two oxygen atoms more than the starting material, has neither aldehyde nor ketone properties, and is not phenolic. On the theory that the aromatic nucleus had been attacked, the substance was given the Formula I, which accounts well for its chemical behavior. By saponification, ozodihydrocodeine is converted to a dibasic acid (II), dihydromorphinic acid,

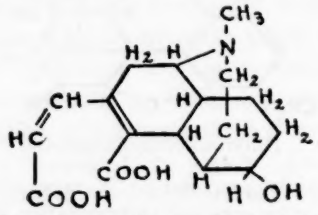


I. Ozodihydrocodeine II. Dihydromorphinic Acid

which is believed to be closely related to the morphinic acid of Wieland and Kapplemaier (129) (p. 145). The latter substance, because of its ketone properties, Speyer proposes to rename morphinonic acid. Additional evidence for the opening of the aromatic nucleus in this ozonization is found in the products from the treatment of dihydroethylmorphine with ozone; a homolog of ozodihydrocodeine, ozodihydroethylmorphine is obtained (Formula I, $COOC_2H_5$ in place of $COOCH_3$), which yields the same dihydromorphinic acid (II) on saponification. Dihydromorphinic acid adds one molecule of hydrogen on catalytic reduction; the exact point of addition is not certain.

Electrolytic reduction of ozodihydrocodeine or ozodihydroethylmorphine resulted in a compound in which hydrolysis of the ester and

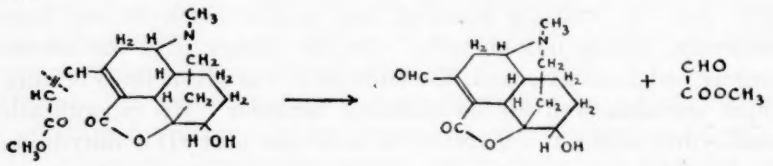
lactone groups, and replacement of the hydroxyl on C-5 by hydrogen had taken place; the compound was therefore named 5-desoxydihydromorphinic acid (194).



5-Desoxydihydromorphinic Acid

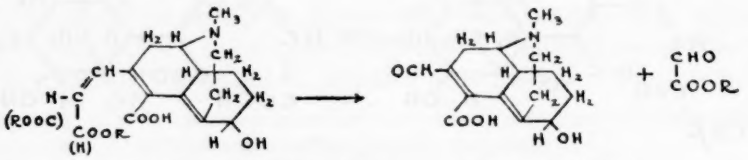
Both ozodihydrocodeine and ozodihydroethylmorphine were found to add one molecule of hydrogen on catalytic hydrogenation, giving products which saponified easily to the before-mentioned 5-desoxydihydromorphinic acid; the addition of hydrogen apparently took place in this case to the lactone group (194).

Ozodihydrocodeine and ozodihydroethylmorphine can be further split by ozone to glyoxylic methyl or ethyl ester and an aldehyde-lactone, dihydrocodinal (195).



Ozodihydrocodeine Dihydrocodinal

Sodium alkylate transforms ozodihydrocodeine into the cis-trans isomeric pair, β- and γ-ozodihydrocodeine. These ozonize to give glyoxylic ester and β-dihydrodiconal (138).



β- and γ-Ozodihydrocodeine β-Dihydrodiconal

Descriptive Part (Codeine)

PREPARATION OF CODEINE FROM MORPHINE BY THE METHOD OF RODIONOV (43)

Dimethylaniline methylbenzenesulphonate is prepared by heating 25 g. of methylbenzenesulphonate with 18 g. of dimethylaniline on a water bath. The mixture solidifies, then melts again with considerable evolution of heat, and hardens to a crystalline mass. The yield is quantitative; recryst. from alcohol, m. p. 180° to 181°. Dimethylaniline methyl-p-toluenesulphonate, m. p. 160° to 161°, is prepared and used for methylation in a similar manner. 4.5 g. of sodium is dissolved in 45 c. c. of absolute alcohol, and to it is added a solution of 55 g. of dimethylaniline methylbenzenesulphonate in 130 c. c. of absolute alcohol. The crystalline sodium benzene sulphonate which separates is filtered off and washed with a little absolute alcohol. The alcoholic filtrate contains phenyltrimethyl-

ammonium hydroxide (dimethylaniline methohydroxide); to it is added 42 g. of anhydrous morphine. The alcohol is distilled from the solution on an oil bath; the temperature is allowed to rise to 110°, and held there for three-fourths to one hour. The mixture is acidified with 15% acetic acid and steam-distilled until all dimethylaniline is removed. After filtering, the flask contents are made alkaline with a large excess of 20% sodium hydroxide; the codeine separates as an oil, which soon crystallizes. The alkaline mother liquors still contain some codeine, which is extracted by benzene. Yield, about 29 g. of codeine; the alkaline solution contains about 9 g. of morphine, which may be regained, making the yield of codeine, based upon the morphine which reacted, 84% to 85%.

I. CODEINE SALTS

CODEINE: $B=C_{18}H_{21}O_3N$. —HYDROCHLORIDE, $B\cdot HCl+2H_2O$, cryst. from water in rosettes of short 4-sided prisms (11), sol. in 20 parts of water at 15.5° (28.5 parts, 15.5° (196)), in less than 1 part of water at 100°. It softens at 132°, becomes again hard, discolors at 260°, melts to brown liquid at 287° (197); m. p. anhydrous 264° (198). In vacuum one molecule of hydrate water is lost at room temperature, the second molecule at 100°, without decomp.; thermochemistry, Leroy (75); $[\alpha]_D^{22.5}=-108.18°$ (66). —PLATINICHLORIDE, $(B\cdot HCl)_2PtCl_4+4H_2O$, fine silky needles, or orange granular cryst., sol. in hot water with partial decomposition (11); from conc. aqueous solution it separates amorphous, then crystallizes with $6H_2O$ (144). —AURICHLORIDE, $B\cdot HCl\cdot AuCl_3$, yellow amorphous precip. (144). —MERCURICHLORIDE, $(B\cdot HCl)_2HgCl_2+H_2O$, grouped colorless needles (144). —STIBNICHLORIDE, $(B\cdot HCl)_2SbCl_5$, red-brown microscopic plates (199). —HYDROBROMIDE: $B\cdot HBr+2H_2O$, tufts of fine white needles from dil. alcohol (4-sided prisms), sol. in 82.5 parts water at 15°. It loses $\frac{1}{2}H_2O$ at 100° and becomes anhydrous at 115° (200) (201); the anhydrous salt melts at 190° to 192°. It is insol. in ether, ligroin, benzene, ethyl acetate, slightly sol. in alcohol, very sol. in boiling water. $[\alpha]_D^{22}=-96.6°$ (water, p=1) (198).

—HYDRIODIDE: $B\cdot HI+H_2O$, needles from water, sol. in 60 parts of cold water (11). It cryst. in white needles from alcohol by addition of ether. It contains $2H_2O$ when cryst. from water, and becomes anhydrous at 100° (144); m. p. 266°. —MERCURIODIDE, $(B\cdot HI)_2HgI_2$ (202), crystalline. —BISMUTHIODIDE, $(B\cdot HI)_3(BiI_3)_4$ (203). —SUPERIODIDE, $B\cdot HI_3$, triclinic violet crystals ("Andersonite") from alcohol (204) (205). A PENTAIODIDE, $B\cdot HI_5$, green-gray feltlike needles, easily converted to the TRIIODIDE, is also known (206). CODEINE TETRACHLORIODIDE, $B\cdot HICl_4$, orange needles from gl. acetic acid (207).

—SULPHATE: $B_2\cdot H_2SO_4+5H_2O$, needles from water, or 4-sided prisms, sol. in 30 parts cold water, 6.6 parts at 80°, in 1,020 parts alcohol 25°, 350 at 60°, insol. in chloroform or ether (11) (53) (144). $[\alpha]_D=-101.2°$ (water, p=3) (66); $n_D=1.560$ (261).

—THIOSULPHATE: $B\cdot H_2S_2O_3+5H_2O$, rhombic prisms, sol. in 18 parts cold water (208).

—NITRATE: $B\cdot HNO_3$, small prisms from water (11).

—PHOSPHATE: $B\cdot H_3PO_4+2H_2O$, ($1\frac{1}{2}$ H_2O), efflorescent needles, sol. in 2.3 parts water at 25°, 3.2 parts at 15° (55), 0.5 parts at 80°; soluble in 260 parts of alcohol, 25°, 100 parts at boiling point; in 6,750 parts chloroform at 25°; in 1,310 parts of ether at 25° (11) (53).

—THIOCYANATE: $B\cdot HCNS$ ($+\frac{1}{2}H_2O$?), grouped needles from water (11) of m. p. 100° (8).

—CHROMATE: $B_2\cdot H_2CrO_4+5H_2O$, yellow needles from hot water (144).

—PERCHLORATE, needles, soluble in water or alcohol; explodes on heating (209).

—HYDRAZOATE: $B\cdot N_3H+2H_2O$, cryst. in needles, loses N_3H and $2H_2O$ at 100° (210).

—HYDROFERRICYANIDE, white precip. from alcoholic solution, becoming cryst. with excess of the acid (8). —HYDROFERROCYANIDE, crystalline precip. (8).

—OXALATE: $B_2 \cdot C_2H_2O_4 + 3H_2O$, sol. in 30 parts water at 15.5° (11) (198).

—ACETATE: $B \cdot C_2H_4O_2 + 2H_2O$, yellow powder, very sol. in water, alcohol, ether, ethyl acetate. Loses acetic acid at 100° (144).

—MONOCHLOROACETATE, m. p. 153° to 154°. —DICHLOROACETATE, m. p. 156°. —TRICHLOROACETATE, m. p. 93°. —MONOCHLOROCROTONATE, $B \cdot C_4H_5O_2Cl$, m. p. 171°. —TRICHLOROBUTYRATE, m. p. 173°. —DIBROMOPYRUVATE, m. p. 70° (211).

—PICRATE, cryst. from 50% alcohol, m. p. 196° to 197° (corr.) (212).

—SALICYLATE: $B \cdot C_7H_6O_3$, anhydrous crystalline powder, diff. sol. in water or alcohol (213) (214).

—p-TOLUENETHIOSULPHONATE: $B \cdot C_7H_7SO_2SH$, white leaflets from alcohol. —α-NAPHTHALENETHIOSULPHONATE, yellow-white cryst. from alcohol. —β-NAPHTHALENETHIOSULPHONATE, cryst. from alcohol (215).

—o-GUAIACOLSULPHONATE: $B \cdot C_6H_3(OH)(OCH_3)SO_3H$, colorless cubic cryst., sol. at 25° in 95 parts water, 450 parts alcohol, 30 parts methyl alcohol, m. p. 164° to 165° (216) (217).

—DIETHYLBARBITURATE (Codeonal), m. p. about 85°, sol. in hot water, alcohol, ether, acetone, chloroform, diff. sol. in benzene (218). —DIALLYLBARBITURATE, m. p. 105°, sol. in water, alcohol, ether, acetone, chloroform, sol. with diff. in benzene (219) (220). —PHENYLETHYLBARBITURATE, white cryst. of m. p. 80°, diff. sol. in water, sol. in organic media (221). —p-ACETAMINOPHENATE, m. p. about 125°, cryst. from water.

CODEINE-NARCOTINE HYDROCHLORIDE, prisms decomp. at 200°, sol. in water, with difficulty in alcohol, insol. in ether (222) (223).

—METHOBROMIDE (Eucodin), $B \cdot CH_3Br$, prep. quantitatively from codeine in dry chloroform with methyl bromide (224), or directly from morphine with KOH and methyl bromide (*cf.* also Riedel A–G (225), Gerber (226)). Coffin-shaped cryst., or hard hexagonal prisms from water or aqueous acetone; m. p. 261°; sol. in 0.75 parts hot water, in 2 to 3 parts cold water, sol. in hot methanol, sparingly in ethyl alcohol, insol. in chloroform or ether.

—METHIODIDE: $B \cdot CH_3I$ (227) from hot water, needles with 2 H_2O (28); cryst. from alcohol, decomp. 270°, $[\alpha]_D^{17} = -81.9°$ (99% alcohol, C=1.139), prep. in 90% yield from morphine with alkali and methyl iodide (228). Nearly insol. in alcohol, sparingly sol. in cold water. Degradation to α-methylmorphimethine, page 276.

—METHOCHLORIDE: $B \cdot CH_3Cl + H_2O$, prisms from conc. aqueous solution; the Platinum salt $(B \cdot CH_3Cl)_2PtCl_4 + 3H_2O$ consists of orange-red crystals (28). —METHOSULPHATE, $B_2 \cdot (CH_3)_2SO_4 + 4H_2O$, rhombic cryst. from water, sol. in hot water, sparingly in alcohol; $[\alpha]_D^{15} = -130.1°$ (water, p.=5) (28). —METHOHYDROXIDE is a noncrystalline, strong base. —METHOMETHYLSULPHITE, (226), crystallizes from absol. alcohol on addition of ether.

—ETHOBROMIDE, $B \cdot C_2H_5Br + 5H_2O$, from codeine in chloroform with diethyl sulphate, then treated with KBr (225). —ETHIODIDE, $B \cdot C_2H_5I$, from codeine in alcohol with ethyl iodide at 100°, white cryst. from water (229). Degradation, Vongerichten and Schrötter (230).

DICODEINE ETHYLENE DIBROMIDE: $B_2 \cdot C_2H_4Br_2 + 4H_2O$, rhombic cryst. of m. p. 177° to 179°, $[\alpha]_D^{20} = -97.06°$ (water) (231). —DICODEINE ETHYLENE DICHLORIDE, $B_2 \cdot C_2H_4Cl_2 + 4H_2O$, colorless needles from water, soften 164° to 168°, melt 182° to 192°. It gives a Platinichloride, $B_2 \cdot C_2H_4PtCl_6 + 7H_2O$, and Aurichloride, $B_2 \cdot C_2H_4AuCl_4$ (144) (231).

CODEINE IODOMETHIODIDE: $B \cdot CH_2I_2$, colorless needles of m. p. 214° to 216°; the IODOMETHOCHLORIDE, $B \cdot CH_2ICl$ cryst. in needles of m. p. 235° to 238° (232).

II. CODEINE ESTERS

FORMYLCODEINE, prep. by refluxing codeine (10 g.) with 100% formic acid (50 g.), 5 to 6 hours; the ester, precipitated with soda and recrystallized from alcohol forms colorless needles of m. p. 180°; it is nearly insol. in water, sol. in chloroform or benzene, sparingly in alcohol or ether. It has also been prepared from chlorocodide with sodium formate, or from codeine with formic esters or formic-acetic anhydride. The HYDROCHLORIDE cryst. in white needles (233) (234) (235).

ACETYLCODEINE: $C_{18}H_{20}O_3N(C_2H_3O)$, from heating codeine with acetic acid or acetic anhydride. It crystallizes in prisms from ether, m. p. 133.5°; sol. in alcohol, ether, chloroform, or benzene, sparingly sol. in boiling water, in which it is slowly hydrolyzed. The HYDROCHLORIDE ($+2H_2O$) is cryst., the PLATINICHLORIDE is an amorphous yellow precip. The ETHIODIDE ($+\frac{1}{2}H_2O$) forms snow-white crystals. The METHOCHLORIDE was prep. by acetylating codeine methochloride; it cryst. anhydrous or with $2H_2O$ and gives a METHOPLATINICHLORIDE as a yellow cryst. powder (28) (236). ACETYLCODEINE METHIODIDE, $C_{20}H_{23}O_4N \cdot CH_3I$, colorless needles from water, m. p. 250° to 252° (decomp.) (165); the METHOHYDROXIDE rearranges to CODEINE METHACETATE. ACETYLCODEINE-o-GUAIACOLSULPHONATE forms white prisms from conc. aqueous solution (216). Acetylcodeine boils at 258° /11 mm.;. it is unchanged by long heating with acetic anhydride at 170° (237).

DIACETYLCODEINE: $C_{22}H_{27}O_5N$, was described by Causse (238), who prepared it by the action of zinc in acetic anhydride with sodium acetate on codeine; prisms, $[\alpha] = -450°$ (alcohol); the METHIODIDE m. at 230° (decomp.), the ETHIODIDE m. p. 245°. According to Knorr (181), Causse's work is incorrect, and only acetylcodeine is obtained from this reaction. The diacetylcodeine of Knoll and Co. (180) is acetoacetylcodeine, *q. v.*

PROPIONYLCODEINE: $C_{18}H_{20}O_3N(C_3H_5O)$, noncrystalline; the HYDROCHLORIDE ($+2H_2O$), cryst. in colorless needles from water, the PLATINICHLORIDE forms yellow crystals. —ACETATE, colorless needles. —HYDRIODIDE ($+H_2O$) needles from water. —NEUTRAL SULPHATE, not cryst. —NEUTRAL OXALATE, crystallizes with $3H_2O$ (28). BUTYRYLCODEINE, noncrystalline, but gives a cryst. —HYDROCHLORIDE, $C_{18}H_{20}O_3N(C_4H_7O) \cdot HCl + 3H_2O$. The ETHIODIDE cryst. with $\frac{1}{2}H_2O$ (159) (239). SUCCINYLCODEINE, $C_{18}H_{20}O_3N(C_4H_5O_3) + 5H_2O$, cryst. from 80% alcohol. The HYDROCHLORIDE cryst. with one molecule of water (147). TARTRYLCODEINE is amorphous, salts amorphous (147). CAMPHORYLCODEINE, $C_{18}H_{20}O_3N(C_{10}H_{15}O_3) + 4H_2O$, cryst. from alcohol. The HYDROCHLORIDE ($+3H_2O$) is crystalline (147).

BENZOYLCODEINE: $C_{18}H_{20}O_3N(C_7H_5O)$, cryst. from ether. The HYDROCHLORIDE cryst. with $1H_2O$ (239). The ETHIODIDE cryst. from 85% alcohol with $\frac{1}{2}H_2O$ (159). The METHIODIDE, needles of m. p. 254° (240).

CODEINE PHENYLCARBAMINIC ESTER, Codeylphenylurethane, from action of phenylisocyanate on codeine, prisms of m. p. 141°, giving a METHIODIDE, $C_{25}H_{26}O_4N_2 \cdot CH_3I$, needles from alcohol, m. p. 255° to 260° (240).

CARBETHOXYCODEINE: $C_{18}H_{20}O_3N(COOC_2H_5)$, cryst. of m. p. 77° to 78°, $[\alpha]_D = -202.8°$ (alcohol), prep. in poor yield from codeine in chloroform with alkali and ethylchlorocarbonate; isolated as the BITARTRATE, $C_{18}H_{20}O_3N(COOC_2H_5) \cdot C_4H_6O_6$, needles from alcohol, m. p. dry 120°, hydrates in air to a compound of m. p. 137° to 140°; $[\alpha]_D = -120.3°$ (water) (241).

III. CODEINE ETHERS

CODEINE METHYL ETHER (Dimethylmorphine): $C_{19}H_{23}O_3N$, prep. by distilling methylcodeine methochloride at 2 mm. (suffers loss of CH_3Cl), or by methylation of codeine-N-oxide, and subsequent treatment with SO_2; prisms from methyl

alcohol, m. p. 140° to 141°; the salts are not crystalline. The N-OXIDE HYDRIODIDE m. 253°. The METHOCHLORIDE forms white crystals from alcohol, m. p. 208°, yielding a Picrate as yellow needles from water, m. p. 211° to 212°, and a Platinichloride in needles decomp. at 215° (182). The Emde degradation (183) of the methochloride gave a des-base (dimethylmorphimethine) of m. p. 91° to 92° (corr.), $[\alpha]_D^{17} = -254.2°$ (methyl alcohol) whose Methiodide showed $[\alpha]_D^{17} = -150°$ (water). (*Cf.* α-methylmorphinethine methyl ether, page 276.) CODEINE METHYL ETHER METHIODIDE, $C_{19}H_{23}O_3N \cdot CH_3I$, cryst. from 80% alcohol, m. p. 257° (263° (242)), $[\alpha]_D^{22} = -107.2°$ (water) (184), $[\alpha]_D^{15} = -109.7°$ (water) (183). Sol. in 2 parts of water, 8 parts of methyl alcohol.

DICODEYLMETHANE, from condensation of codeine in hydrochloric acid with formaldehyde; a varnishlike solid, of whose structure nothing is known. The HYDROCHLORIDE decomp. 140°, sol. in water or alcohol, no color with $FeCl_3$ (243).

IV. MISCELLANEOUS DERIVATIVES

CODEINE-N-OXIDE: $C_{18}H_{21}O_4N$, prep. from codeine with 30% H_2O_2, rectangular tablets from water, m. p. 230° to 231°; the HYDROBROMIDE m. 196°, the NITRATE m. 187°, HYDROCHLORIDE and ACETATE, crystalline (135). Conversion to norcodeine, Diels and Fischer (136). A dimolecular codeine oxide (hydrate) $C_{36}H_{44}O_9N_2 + 7H_2O$ is described by Mossler and Tschebull (137) from codeine with 3% H_2O_2, crystals of m. p. 200° to 202°, $[\alpha]_D^{20} = -97.6°$ (water, C=2.51), $[\alpha]_D^{19} = -107.2°$ (alcohol, C=2.51). The dimolecular compound is broken up by hydrochloric acid, giving $C_{18}H_{21}O_4N \cdot HCl + H_2O$, of m. p. 219° to 220°, $[\alpha]_D^{20} = -105.8°$ (water, C=2.05), which yields a free base $C_{18}H_{21}O_4N + H_2O$ of m. p. 215°, $[\alpha]_D^{18} = -97.1°$ (water, C=2.08). The free base reduces to codeine with sulphur dioxide.

CODEINE-N-OXIDE SULPHONIC ACID: $C_{18}H_{20}O_4NSO_3H$, from codeine oxide with acetic anhydride-sulphuric acid, crystalline powder of m. p. 272°, $[\alpha]_D^{20} = -115.4°$ (2 *N* KOH, C=4.17). It forms a crystalline potassium salt. Sulphur dioxide converts it to codeine sulphonic acid; water at 180° converts it to codeine; cold conc. sulphuric acid converts it to β-codeine sulphonic acid (128) (163) (244). Oxidation with potassium dichromate gives norcodeine sulphonic acid (136). By catalytic reduction, dihydrocodeine sulphonic acid (p. 198) is obtained (192). α-CODEINE-N-OXIDE SULPHONIC ACID, $C_{18}H_{20}O_4NSO_3H$, an isomer of codeine-N-oxide sulphonic acid, is formed under slightly different conditions; it is more soluble in water or organic media, and has a different crystal form. It is converted by dil. sodium hydroxide or sulphuric acid to codeine oxide sulphonic acid. With SO_2 it gives codeine sulphonic acid, with water at 160°, codeine. Nitric acid gives nitro-α-codeine oxide sulphonic acid, $C_{18}H_{19}O_4N(SO_3H)NO_2$, yellow plates decomp. 167° to 170°, which warm sulphurous acid converts to α-nitrocodeine (m. p. 197°). Bromine water with α-codeine oxide sulphonic acid gives a substance of unknown structure, $C_{15}H_{17}O_4Br_3$, needles of m. p. 258° to 260° (decomp.) (128) (163). Catalytic reduction gives α-dihydrocodeine sulphonic acid (192) (p. 198).

CODEINE SULPHONIC ACID: $C_{18}H_{20}O_3NSO_3H + 2H_2O$, prep. by reduction of codeine-N-oxide sulphonic acid, needles or prisms decomp. above 300°, $[\alpha]_D^{20} = -136.3°$ (2 *N* KOH, C=4.23). It is converted by water at high temp. into codeine, by H_2O_2 into codeine-N-oxide sulphonic acid. The action of conc. nitric acid gives nitrocodeine (m. p. 217°); cold conc. H_2SO_4 gives a cryst. comp. of decomp. p. 285° to 290°. With methyl iodide and alkali, CODEINE SULPHONIC ACID METHOHYDROXIDE, needles from water, decomp. 284°, $[\alpha]_D^{20} = -63.2°$ (water, C=1.76) is obtained (128) (163), which has also been prepared by methylation of morphine sulphonic acid (245). Catalytic reduction gives dihydroco-

deine sulphonic acid (192). β-CODEINE SULPHONIC ACID, $C_{18}H_{20}O_3NSO_3H$ (?), prep. from codeine-N-oxide sulphonic acid with conc. sulphuric acid; plates decomp. about 243°, $[\alpha]_D^{20} = -190.1°$ (water containing a drop of KOH, C= 3.02) (128). γ-CODEINE SULPHONIC ACID, $C_{18}H_{20}O_3NSO_3H$ (?), prep. from β-codeine sulphonic acid by heating with sulphurous acid, needles from 50% alcohol, decomp. about 280° (128).

NITROCODEINE (11): $C_{18}H_{20}(NO_2)O_3N$, prep. from 100 g. codeine in 300 c. c. gl. acetic acid, to which 100 c. c. of conc. nitric acid, sp. gr. 1.4, is slowly dropped, with good cooling; diluted to 2 liters and precip. with ammonia. Cryst. from alcohol, m. p. 221° to 222° (127). Prep. also from codeine sulphonic acid by heating with conc. nitric acid (128) (163). The HYDROCHLORIDE is not cryst. —PLATINICHLORIDE $(C_{18}H_{20}O_5N_2 \cdot HCl)_2PtCl_4 + 4H_2O$. —SULPHATE, needles $(C_{18}H_{20}O_5N_2)_2H_2SO_4$. —OXALATE, yellow prisms (11). The crystalline METHIODIDE gives with alkali NITROMETHYLMORPHIMETHINE, yellow needles from dil. alcohol, m. p. 214° to 215°, which forms a cryst. Methiodide whose further degradation was unsuccessful (246). ACETYLNITROCODEINE, yellow leaflets of m. p. 203°, sol. with diff. in alcohol (193). ACETYLCYANONORNITROCODEINE, m. p. 222°, from the action of cyanogen bromide on acetylnitrocodeine (193) (247). On saponification it gives CYANONITRONORCODEINE, cryst. from alcohol, m. p. 236° to 238°, which is also obtained when cyanonorcodeine is nitrated (193). 2-NITRONORCODEINE, yellow cryst. of m. p. 185°, diff. sol. in alcohol; its Hydrochloride is crystalline, its Nitroso compound melts at 236°, its Diacetyl derivative melts at 251° (177) (193). NITRO-N-ISOAMYLNORCODEINE, m. at 90°, and its Acetyl derivative m. 62° (247).

α-NITROCODEINE: $C_{18}H_{20}(NO_2)O_3N$, from nitration of α-codeine oxide sulphonic acid, and reduction of the nitro-α-codeine oxide sulphonic acid with sulphurous acid; quadratic plates from alcohol, m. p. 197°. It reduces to the same aminocodeine as is obtained when nitrocodeine is reduced (128) (163).

2-AMINOCODEINE: $C_{18}H_{20}(NH_2)O_3N$, from reduction of nitrocodeine with tin and hydrochloric acid (129), or acetic acid (246), stannous chloride (248), or electrolytically (128); cryst. from absol. alcohol in plates, m. p. 226° (228°). The HYDROCHLORIDE, decomp. about 290°, separates when the hydrochloric acid solution is made ammoniacal (128). DIACETYLAMINOCODEINE, from acetylation of aminocodeine, cryst. from methyl alcohol in white needles, m. p. 120°. Its METHIODIDE m. 251° to 252°, gave on morphol degradation (acetic anhydride and silver acetate) a Triacetylaminomethylmorphol, m. p. 178° to 179° (246). AMINONORCODEINE, $C_{17}H_{20}O_3N_2$, cryst. from alcohol, m. p. 221°. The HYDROCHLORIDE decomp. 235°, PLATINICHLORIDE cryst. in leaflets. TRIACETYL derivative, m. p. 160° to 162°. AMINOCYANONORCODEINE, $C_{18}H_{19}O_3N_3$, needles of m. p. 288°. Its HYDROCHLORIDE is not melted at 300°. PLATINICHLORIDE, crystalline (193).

NITROCODEIC ACID (127): $C_{16}H_{18}O_9N_2$, prep. by oxidation of nitrocodeine or nitropseudocodeine with conc. nitric acid (sp. gr. 1.30) for four days; isolated through the lead salt. The free base precip. from the hydrochloride with sodium acetate consists of fine needles, slightly sol. in alcohol, decomp. without melting. The HYDROCHLORIDE cryst. from dilute HCl in yellow needles. BARIUM SALT, $C_{16}H_{16}O_9N_2Ba \cdot 2H_2O$. POTASSIUM SALT, golden-yellow needles. Esterification takes place with loss of a molecule of water. The METHYL ESTER cryst. from dil. methyl alcohol in flat light-sensitive leaflets, $C_{17}H_{18}O_8N_2 + 2CH_3OH$, optically inactive; it probably has a betaine structure. Its Hydrochloride cryst. in needles. The ETHYL ESTER was isolated as the Hydrochloride. By the action of diazomethane on nitrocodeic acid, $C_{19}H_{22}O_8N_2$ (?) is obtained, structure uncertain, yellow prisms, m. p. 180°, containing 3 methoxyl groups. The action of conc. HCl at 150° on nitrocodeic acid gives NORNITROCODEIC ACID, $C_{15}H_{16}O_9N_2$, needles.

AMINOCODEIC ACID (127), is obtained as the HYDROCHLORIDE, $C_{16}H_{20}O_7N_2 \cdot HCl$ by reduction of nitrocodeic acid. By treatment of nitrocodeic acid with hot hydriodic acid, NORAMINOCODEIC ACID, $C_{15}H_{18}O_7N_2$, is obtained.

2-HYDROXYCODEINE: $C_{18}H_{21}O_4N + H_2O$, prep. by boiling diazocodeine with water; cryst. in needles from alcohol, m. p. 176° (129); sinters at 176°, melts at 234° (128). The base is soluble in alkali. The HYDROCHLORIDE cryst. with two molecules of water. (*Cf.* Ferrein (248).)

9-HYDROXYCODEINE: $C_{18}H_{21}O_4N$, prep. by oxidation of codeine in dil. sulphuric acid with potassium dichromate at 5° (119), maximum yield about 10% (121). Crystallized from benzene or acetic acid it melts at 207° to 208°; soluble in chloroform, sparingly so in alcohol, acetone, or ether. —HYDROCHLORIDE, cryst. from water. —PICRATE, from water, m. p. 166°. —PICRONOLATE, from alcohol, m. p. 170° (121). —METHIODIDE, $C_{18}H_{21}O_4N \cdot CH_3I + CH_3OH$, decomp. 240° to 250°. It degrades with NaOH to KETODIHYDROMETHYLMORPHIMETHINE, an oily base, which with ether yields crystals, $C_{19}H_{23}O_4N + C_4H_{10}O$, m. p. 50° to 60°. Its Hydrochloride decomp. about 246°, the Hydriodide m. 220°, Picrate m. 211°, Picronolate decomp. 140°, Oxime hydrochloride, m. p. 279°, Oxime methiodide, m. p. 270°, Semicarbazone, m. p. 106° to 107°, Acetyl derivative, m. p. 81° (whose hydriodide m. 270°, hydrobromide m. 280° to 285°, and methio dide decomp. 260°). KETODIHYDROMETHYLMORPHIMETHINE METHIODIDE ($+1\frac{1}{4}$ H_2O) m. at 220°, and decomp. with acetic anhydride to ethanoldimethylamine and methoxydiacetoxyphenanthrene (121) (125) (126). DIACETYLHYDROXYCODEINE cryst. from alcohol and m. at 160° to 161°. Its HYDRIODIDE m. 230°, METHIODIDE m. 248° to 255° (119) (125). NITROHYDROXYCODEINE, prep. from hydroxycodeine in acetic acid with nitric acid, cryst. from methanol, decomp. 232° (127).

7- or 14-HYDROXYCODEINE: $C_{18}H_{21}O_4N$, is formed together with hydroxythebainol by reduction of hydroxycodeinone (p. 256) with zinc dust in 85% formic acid. It cryst. from a chloroform-alcohol mixture in prisms of m. p. 293°, $[\alpha]_D^{20} = -119.5°$ (dil. acetic acid, C=2.065). It is insoluble in alkali, and forms no oxime. The HYDROCHLORIDE is crystalline; HYDROBROMIDE decomp. 290°. MONOACETYLHYDROXYCODEINE decomp. 265° and gives a Methiodide decomp. 265°. HYDROXYCODEINE could not be hydrogenated with palladium catalyst (131) (132) (249).

CHLOROCODEINE: $C_{18}H_{20}O_3NCl + 1\frac{1}{2}H_2O$, prep. by treatment of codeine hydrochloride with potassium chlorate at 65° to 70° (11), or better by the action of 30% hydrogen peroxide on codeine hydrochloride in 30% formic acid; cryst. from absol. alcohol in needles of m. p. 175° to 176°, $[\alpha]_D^{16} = -147.21°$ (alcohol, C= 1.0048) (164). Sparingly soluble in hot water or ether, soluble in alcohol. The HYDROCHLORIDE cryst. in concentric-grouped needles, sol. in water, and gives an amorphous Platinichloride. The SULPHATE ($+4H_2O$) cryst. in short prisms. The base is reduced with hydrogen and palladium to CHLORODIHYDROCODEINE, $C_{18}H_{22}O_3NCl$, octahedra from alcohol, m. p. 196° (164).

DICHLOROCODEINE, chlorochlorocodide, results from the action of phosphorous pentachloride on chlorocodeine, and has not been further described. It differs from the dichlorocodeine obtained when an excess of PCl_5 acts on codeine at 70 °; the latter, $C_{18}H_{19}O_2NCl_2$, cryst. in colorless sparkling rhombic prisms from alcohol, m. p. 196° to 197°. Insoluble in water, sol. in alcohol, ether, chloroform, benzene, sparingly in petroleum ether. The HYDROCHLORIDE cryst. in concentric-grouped hydrated needles, decomp. about 160° to 170°; it gives a red-brown ferric chloride reaction. The PLATINICHLORIDE cryst. in anhydrous yellow needles from dil. hydrochloric acid (162).

BROMOCODEINE: $C_{18}H_{20}O_3NBr$ ($+\frac{1}{2}H_2O$, or $1\frac{1}{2}H_2O$), prep. by treating codeine suspended in water with bromine-water (11) (162), or by the action of 30%

hydrogen peroxide on a solution of codeine hydrobromide in 30% formic acid (164). Cryst. from dil. alcohol in small pointed prisms of m. p. 161° to 162° (freshly prepared, it melts in its hydrate water on gentle heating); sparingly sol. in hot water, nearly insoluble in ether, soluble in alcohol or ammonia. —HYDROCHLORIDE, grouped needles. —HYDROBROMIDE ($+H_2O$), small prisms sol. in hot water. —PLATINICHLORIDE, yellow precip. (11). A BROMOCODEINE DIBROMIDE, $C_{18}H_{20}O_3NBr_3$, m. p. 200°, from bromination of codeine-N-oxide sulphonic acid, was obtained by Speyer and Krauss (250). BROMOCODEINE METHIODIDE, from bromomorphine methohydroxide with methyl iodide, or bromocodeine with methyl iodide; prisms containing one molecule of hydrate water, m. p. 242° to 244°. On treatment with alkali it degrades to BROMOMETHYLMORPHIMETHINE (165), $C_{19}H_{22}O_3NBr$, cryst. from dil. methyl alcohol, m. p. 132°, which when heated to 170° to 180° rearranges to an isomer of m. p. 182° to 184°. The Platinichloride of the 132° form cryst. with $4H_2O$ and the Methiodide of the same form is sparingly sol., m. p. 252°; further degradation products not crystalline. BROMOCODEINE METHOCHLORIDE ($+2\frac{1}{2}H_2O$), needles from water (165). BROMOCODEINE ETHIODIDE, degradation (230).*

BROMOCHLOROCODIDE (162), see page 222.

BROMODIHYDROCODEINE: $C_{18}H_{22}O_3NBr$, from catalytic reduction of bromocodeine; cryst. from alcohol in octahedra of m. p. 190°. Further hydrogenation converts it to dihydrocodeine (164).

TRIBROMOCODEINE: $C_{18}H_{18}O_3NBr_3$. An amorphous base of this formula, and amorphous salts, were described by Anderson (11).

DIIODOCODEINE: $C_{18}H_{19}O_3NI_2$, from treatment of a conc. solution of codeine hydrochloride with iodine chloride; yellow crystalline precip. —PLATINICHLORIDE ($+H_2O$), yellow precip. (168). CODEINE TRIIODIDE (Superiodide), see page 189.

CHLOROCODIDE, BROMOCODIDE, IODOCODIDE, and their derivatives, see pages 221 ff.

DICYANOCODEINE: $C_{20}H_{21}O_3N_3$, from codeine and cyanogen in alcohol solution, colorless cryst. from alcohol-ether, readily decomp. with liberation of cyanogen. Forms salts; nothing is known of its structure (11).

SODIUM CODEINE: $C_{18}H_{20}O_3NNa$, from the action of sodium on anhydrous codeine in benzene, brown-yellow powder, sol. in water or alcohol, insol. ether, benzene, chloroform (170).

POTASSIUM CODEINE: $C_{18}H_{20}O_3NK$, voluminous crystalline mass, sol. in water, alcohol, insol. ether, benzene, chloroform (170).

CODEINE CARBON SUBOXIDE: $C_{18}H_{21}O_3N(C_3O_2)_5$, orange-yellow powder, m. unsharp 155° to 160° (decomp.).

ACETOCODEINE: $C_{20}H_{23}O_4N$, from saponifying acetoacetylcodeine with alcoholic NaOH; cryst. from ethyl acetate, m. p. 150°, $[\alpha]_D^{21} = -141°$ ($CHCl_3$, C=4.58). The OXIME is not crystalline, decomp. about 100°. The METHIODIDE cryst. from water or dil. alcohol in needles or leaflets decomp. about 235°, $[\alpha]_D^{15} = -64°$ (water, C=1.03); it degrades to aceto-β-methylmorphimethine, needles from ethyl acetate, m. p. 149°, $[\alpha]_D^{21} = +150°$ ($CHCl_3$, C=5.66). The acetyl derivative, ACETOACETYLCODEINE, is formed when codeine is heated with acetic anhydride-sulphuric acid mixture at 85°; crystals from alcohol, m. p. 145° to 146°, $[\alpha]_D^{17} = -207°$ ($CHCl_3$, C=5.7), soluble in alcohol, benzene, sparingly in ether, or water. Acetoacetylcodeine oxime cryst. from alcohol in colorless needles with $\frac{1}{2}C_2H_5OH$, m. p. 176° to 178° (180) (181). ACETOACETYL-β-METHYLMORPHIMETHINE METHIODIDE, m. p. 180° to 182°.

NORCODEINE (N-demethylocodeine): $C_{17}H_{19}O_3N$, prep. by treatment of acetylcodeine with cyanogen bromide and hydrolysis of the resulting cyanoacetylnorcodeine (176) (177); from codeine with azodicarboxylic ester, in 40% yield

* See Appendix, p. 362.

(179); from treatment of codeine with nitrous acid and decomp. of the resulting nitrosonorcodeine with alcoholic hydrochloric acid (178); from codeine-N-oxide with potassium chromate (136). The free base forms leaflets or needles from acetone or ethyl acetate, m. p. 185° (186°). The HYDROCHLORIDE ($+3H_2O$), m. at 309° —PLATINICHLORIDE, anhydrous, m. p. 239°. The HYDRIODIDE ($+2H_2O$) melts at 257°. The PICRATE is poorly crystallized. The THIOCARBANILIDE, colorless crystals from alcohol, m. at 210°. NITROSONORCODEINE, yellow pyramids or plates from dil. alcohol, m. p. 246° (176) (178). DIACETYLNORCODEINE, cryst. from alcohol, m. p. 176° to 178° (179). ACETYLCYANONORCODEINE, cryst. from alcohol, m. p. 184°; with hydrochloric acid it gives CYANONORCODEINE, a powder, sparingly sol. in alcohol, m. p. 262° (176) (177).

NORCODYLHYDRAZINE: $C_{17}H_{20}O_3N_2$, from reduction of nitrosonorcodeine; cryst. from alcohol, m. p. 174°. $[\alpha]_D^{20} = +136°$ (chloroform). The HYDROCHLORIDE ($+2H_2O$) m. 135°, anhydrous, m. p. 182° to 185°, $[\alpha]_D^{20} = +116°$ (alcohol). The TETRAZONE, m. 232°, hydrolyzes to norcodeine hydrochloride (193).

NORCODEINE SULPHONIC ACID: $C_{17}H_{18}O_3NSO_3H$ (136), the codeine oxide sulphonic acid hydrate of Freund and Speyer (128), decomp. about 335°; it is converted to norcodeine by heating with water 8 hours at 180°.

NITRONORCODEINE, AMINONORCODEINE, and derivatives, see nitrocodeine, page 193.

N-SUBSTITUTED NORCODEINES: N-METHYL—is identical with codeine. N-ETHYL— (isodionin), m. p. 203°. N-PROPYL— is an oil, giving a cryst. HYDROCHLORIDE of m. p. 185°, and a PLATINICHLORIDE of m. p. 216°. N-n-BUTYL—, m. p. 100°, giving a PLATINICHLORIDE of m. p. 205°. The N-ISOAMYLNORCODEINE is an oil, whose PICRATE m. 100°, PLATINICHLORIDE ($+3H_2O$) m. p. 207°. N-BENZYL— melts below 60°. N-ALLYLNORCODEINE, m. p. 95°, reducible to N-propylnorcodeine; its HYDROCHLORIDE m. 125°, its PLATINICHLORIDE, m. p. 214°, ALLYLIODIDE decomp. 208°. N-HYDROXYETHYLNORCODEINE, needles of m. p. 197° (247) (251). N-PHENYLETHYLNORCODEINE, m. p. 114°; its HYDROCHLORIDE cryst. in scales, m. p. 277°; PLATINICHLORIDE, m. p. 216° to 217° (176). N-PROPARGYL—, m. p. 95°, anhydrous, m. p. 137°; its METHIODIDE decomp. 172°, its bromination product (Br in the aromatic ring of codeine) melts at 100° to 102°. N-DIBROMALLYL—, white powder m. p. about 60°. N-CYCLOPROPYLMETHYL—, not cryst., the HYDROCHLORIDE m. 250° to 252°, PLATINICHLORIDE decomp. 199° to 200°. N-CYCLOBUTYLMETHYL—, not cryst., HYDROCHLORIDE, m. p. 150°, PLATINICHLORIDE, decomp. 217°. N-β-CYCLOPROPYLETHYL—, not cryst., HYDROCHLORIDE decomp. 160°. N-CYCLOPENTYLMETHYL—, m. p. 50°, PICRATE m. p. 125° to 128°, HYDROCHLORIDE, m. p. 171° to 174°. N-CYCLOHEXYLMETHYL—, m. p. 55° to 60°, HYDROCHLORIDE m. p. 171° to 176°, PICRATE 132° to 135°. N-CYCLOHEPTYLMETHYL—, m. p. 59° to 61°, PICRATE, m. p. 139°. N-α-THENYL—, powder of m. p. 76°, HYDROCHLORIDE decomp. about 200°, PICRATE m. about 145° (252). N-β-BUTENYL—, m. p. 44°; the HYDROCHLORIDE m. 128°, the PLATINICHLORIDE m. 198° to 200° (253). N-CYCLOPENTENYL—, isolated as the HYDROCHLORIDE, m. p. 188° (254). N-CINNAMYL—, m. p. 78°, PLATINICHLORIDE decomp. 208° (255). N-γ-BENZOYLOXYPROPYL—, from γ-benzoyloxypropylbromide on norcodeine, m. p. 47°; the PICRATE m. 118° to 119°, the METHIODIDE m. 169° to 170°. On hydrolysis it gives N-γ-HYDROXYPROPYLNORCODEINE, m. p. 133°, PICRATE in yellow leaflets, m. p. 120° to 121°. N-p-NITROPHENYL—, m. p. 212°. N-o,p-DINITROPHENYL—, deep yellow cryst. of m. p. 265°; it reduces to N-o,p-DIAMINOPHENYLNORCODEINE, m. p. 233°, whose Triacetyl derivative m. 144° to 146°. The latter gives with BrCN an unsat. Cyanamide of m. p. 148° to 149°, which hydrolyzes to a base $C_{24}H_{24}O_3N_4$, m. p. 168° to 169°, apparently of the α-methylmorphimethine type.

DIMETHYLAMINOCYANONORCODIDE, from the action of dimethylamine on α-chlorocyanonorcodide (p. 222), cryst. from dil. alcohol, m. p. 192°; its HYDRO-

CHLORIDE m. 266°, PICRATE 190°, METHIODIDE 203°. Hydrolysis of the cyano group gives DIMETHYLAMINONORCODIDE, m. p. 128°, whose PICRATE m. 218°, and PLATINICHLORIDE m. 275° to 276°. DIMETHYLAMINO-N-β-HYDROXYETHYLNORCODIDE, hygroscopic cryst. of m. p. 85°, PLATINICHLORIDE m. 255° (256).

NORCODEINIUM-PIPERIDINIUM IODIDE, from norcodeine with α, ε-diiodopentane, m. p. 272°, PLATINICHLORIDE m. p. 215°. NORCODEINIUM-MORPHOLINIUM IODIDE, from norcodeine with β, β′-diiodoethyl ether, needles of m. p. 255° to 256°, whose PLATINICHLORIDE m. 216°. NORCODEINIUM-DIHYDROISOINDOLIUM BROMIDE, from norcodeine with o-xylylene bromide, needles of m. p. 262°, whose PLATINICHLORIDE m. 233° (257).

DIHYDRONORCODEINE and its derivatives, see Dihydrocodeine.

V. DIHYDROCODEINE

DIHYDROCODEINE (Paracodin): $C_{18}H_{23}O_3N$ ($+H_2O$ (186), $+2H_2O$ (189)), prep. by reduction of codeine, or its salts, with hydrogen in the presence of palladium or platinum (186) (187) (191). It has also been obtained by catalytic reduction of neopine (134), and by catalytic reduction of bromocodeine (164), by Clemmensen reduction of dihydrocodeinone (189) and by methylation of dihydromorphine (188) or of dihydromorphine-N-oxide with dimethyl sulphate and alkali (35). It crystallizes from water or very dilute methyl alcohol (*cf.* Wieland (190), 80% methyl alcohol) in rhombic octahedra containing one molecule of water, m. p. 62° to 63° (186) (65°) (187). The m. p. 55° has also been given (118) (134). Mannich (189) found that the base with two molecules of hydrate water exists in two forms, m. p. 55° and 87° to 88° (Freund (191) 86° to 88°). Anhydrous, it melts at 112° to 113° (134) (189) (190). The 55° base shows $[\alpha]_D = -125°$ (96% alcohol, C=0.2) (118). Dihydrocodeine distills at 248° /15 mm. With conc. hydriodic acid it is converted to dihydromorphine (189). The aromatic ring is opened by ozone (Speyer (194), see below). —HYDROCHLORIDE, from addition of ethereal HCl to an alcoholic solution of the base, cryst. of m. p. 256° (brown) (190). —DIALLYLBARBITURATE, cryst. of m. p. 95°, sol. in hot water, alcohol, acetone, chloroform (218) (219). —ACID TARTRATE, $C_{18}H_{23}O_3N \cdot C_4H_6O_6 + H_2O$ (Paracodin tartrate), colorless cryst. of m. p. 187° to 189°, sol. in 4.5 parts of water, sparingly sol. in alcohol, insol. in ether (214). —METHIODIDE, $C_{18}H_{23}O_3N \cdot CH_3I$, cryst. from alcohol m. p. 257°. On treatment with alkali, it degrades to an oily base, DIHYDROMETHYLMORPHIMETHINE (des-N-methyldihydrocodeine), whose cryst. HYDROCHLORIDE m. 133°, and whose METHIODIDE melts at 160° (173° to 176°).[79] Further degradation did not give crystalline products. Hydrogenation of dihydromethylmorphimethine gives tetrahydromethylmorphimethine (Hydrochloride, m. p. 226°, Methiodide, $C_{19}H_{27}O_3N \cdot CH_3I + H_2O$, m. p. 221° to 224°), identical with that from reduction of the isomeric dihydromethylmorphimethine, or of α- and β- methylmorphimethines. (See p. 277.) Further degradation gave only amorphous products (190) (191).

ACETYLDIHYDROCODEINE: $C_{18}H_{22}O_2N(OCOCH_3)$, from the action of acetic anhydride on dihydrocodeine; cryst. from ether with petroleum ether, m. p. 120° (176) (177).

ACETYLCYANODIHYDRONORCODEINE, from treatment of acetyldihydrocodeine with cyanogen bromide; needles from alcohol, m. p. 227° to 228°. By hydrolysis it gives CYANODIHYDRONORCODEINE, a powder soluble in alcohol, m. p. 213° to 214°, which hydrolyzes further to DIHYDRONORCODEINE, $C_{17}H_{21}O_3N$, cryst. from alcohol, m. p. 194°. Dihydronorcodeine is also obtained when norcodeine is reduced catalytically. The cryst. Hydrochloride m. at 295° (300°) (176) (177) (193), the Platinichloride cryst. in thick red needles, decomp. 245°. The N-ni-

[79] This dihydromethylmorphimethine differs from the hydromethylmorphimethine of Vongerichten (258), which gave a methiodide of m. p. 263°. (See p. 271).

troso derivative cryst. from water or dil. alcohol, and m. at 198° (193); it is also obtained when dihydrocodeine is treated with nitrous acid (178). N-ALLYLDIHYDRONORCODEINE, is an oil. Its Allyl iodide m. at 157° and degrades by the Hofmann method to an oil whose allyl iodide m. 173°, platinichloride m. p. 78° (247) (251). NORDIHYDROCODEINIUM-PIPERIDINIUM IODIDE, from the action of diiodopentane on dihydronorcodeine, m. at 271° (257).

DIHYDROCODEINE METHYL ETHER (Dihydromorphine dimethyl ether): $C_{19}H_{25}O_3N$, from catalytic reduction of morphine dimethyl ether (182). It is identical with TETRAHYDROTHEBAINE, and may be obtained by reduction of thebaine; methylation of dihydrocodeine with trimethylphenylammonium hydroxide was unsuccessful (130). The base cryst. from ether or petroleum ether (b. p. 70° to 80°) in thick prisms of m. p. 83°, $[\alpha]_D^{18} = -153.4°$ (absol. alcohol, C=1.450). —HYDROCHLORIDE ($+3H_2O$) needles of m. p. 115° to 116° from acetone with a little water; —PICRATE, m. p. 222°. —METHIODIDE, cryst. from water, m. p. 135° to 140°, melting again at 212°. Demethylating agents, as hydriodic acid or aluminum chloride convert dihydrocodeine methyl ether to dihydromorphine (259).

DIHYDROCODEINE-N-OXIDE: $C_{18}H_{23}O_4N$, from dihydrocodeine with 30% hydrogen peroxide; precip. from alcohol by absol. ether in rhombic crystals, decomp. 225°. —HYDROCHLORIDE, m. p. 217°. PICRATE, m. p. 161° to 162° (192).

DIHYDROCODEINE SULPHONIC ACID: (192) $C_{18}H_{22}O_3N(SO_3H)$, is known in two forms. The "ordinary" modification results from catalytic reduction of codeine sulphonic acid, or codeine-N-oxide sulphonic acid, or sulphonation of dihydrocodeine-N-oxide. Cryst. in 6-sided leaflets, or prisms (dimorphous) from dil. alcohol, browns at 300°, decomp. 330° to 340°; $[\alpha]_D^{20} = -76.7°$ (weakly alkaline solution, C=2.00). The METHOHYDROXIDE cryst. from dil. alcohol in plates decomp. 280° to 285° (192) (245). Dihydrocodeine sulphonic acid, with water at 150° or with stannous chloride and HCl at 100°, loses the sulphonic acid group, giving dihydrocodeine (192). DIHYDROCODEINE-N-OXIDE SULPHONIC ACID, prisms, m. p. 273° to 275° (192). Action of bromine water, followed by reduction with SO_2, gives $C_{18}H_{22}O_3NBr$, whose Methiodide decomp. 230° (250).

α-DIHYDROCODEINE SULPHONIC ACID: $C_{18}H_{22}O_3N(SO_3H) + H_2O$, prep. by catalytic reduction of α-codeine oxide sulphonic acid; precip. from absol. alcohol with absol. ether as a cryst. powder, decomp. 315° to 320°. $[\alpha]_D^{20} = -88°$ (water, C=1.43). Heated with water at 150° to 160°, it gives dihydrocodeine. Its METHOHYDROXIDE is identical with that obtained from the "ordinary" form. By nitration, α-nitrodihydrocodeine is formed (192).

NITRODIHYDROCODEINE: $C_{18}H_{22}O_3N(NO_2)$, prep. by nitration of dihydrocodeine (191), or of dihydrocodeine sulphonic acid (192); yellow double pyramids from alcohol, m. p. 221°. The α-form, from nitration of α-dihydrocodeine sulphonic acid cryst. in fine yellow needles from absol. alcohol, and m. at 180° (192).

CHLORODIHYDROCODEINE, BROMODIHYDROCODEINE (164), see chloro-and bromocodeine, pages 194, 195.

CHLORODIHYDROCODIDE (191), see chlorocodide, page 223.

DIHYDROXYDIHYDROCODEINE (120): $C_{18}H_{23}O_5N$, prep. by the action of $KMnO_4$ on codeine, in very small yield. It cryst. from absol. alcohol in colorless diamond-shaped plates, m. p. 208° to 209°; sol. in water, sparingly sol. in ether, benzene, cold absolute methyl, or ethyl alcohol. No cryst. salts or alkyl halides could be prepared. The TRIACETYL derivative cryst. from methyl alcohol in colorless plates, m. p. 200°; it contains three acetyl groups, and is a strong base; its Perchlorate cryst. from water in needles, m. p. 281°.

OZO-DIHYDROCODEINE, prep. by ozonization of dihydrocodeine in solution in 25% formic acid; the base is a reddish-yellow oil. —HYDROCHLORIDE, $C_{18}H_{23}O_5N \cdot HCl$, needles from alcohol with a few drops of water, decomp. 242°, $[\alpha]_D^{16} = +77.6°$,

+78.6° (water, C=5.00). —HYDRIODIDE, cryst. from water, decomp. 248° to 250°. —HYDROBROMIDE, rhombic cryst., decomp. 238°. —PICRATE, decomp. 238° to 239°. —METHIODIDE, sinters 152°, decomp. 155°. ACETYL-OZO-DIHYDROCODEINE, oily, giving a Picrate decomp. 208° to 209°. CHLORO-OZO-DIHYDROCODEINE, $C_{18}H_{22}O_4NCl$, needles from 96% alcohol, m. p. 157° to 158°, giving a Picrate decomp. 249° to 250°. Reduction of ozo-dihydrocodeine with zinc and acetic acid gave a small amount of an oily base, isolated as the Hydrochloride, $C_{18}H_{27}O_5N \cdot HCl$, nature unknown. OZO-DIHYDROETHYLMORPHINE, page 162.

DIHYDROMORPHINIC ACID: $C_{17}H_{23}O_6N$, from the action of KOH on ozo-dihydrocodeine or ozo-dihydroethylmorphine, needles from alcohol, decomp. 227°; $[\alpha]_D^{16} = +30.9°$ (water, C=1.84). It is probably closely related to morphinic acid (194). TETRAHYDROMORPHINIC ACID, $C_{17}H_{25}O_6N$, prep. by catalytic reduction of the dihydro compound; cryst. from alcohol, m. p. 217° to 218° (194).

α-CHLOROMORPHINIC ACID (138), see page 222.

5-DESOXYDIHYDROMORPHINIC ACID (194): $C_{17}H_{23}O_5N$ is formed when ozo-dihydroethylmorphine, or ozo-dihydrocodeine, is reduced electrolytically; needles from alcohol with a few drops of water, decomp. 248°; $[\alpha]_D^{17} = +28.3°$ (water, C=5.00); the PICRATE cryst. in needles from alcohol, decomp. 222° to 223°. The 3-METHYL ESTER (194) is obtained by reduction of ozo-dihydrocodeine with palladium and hydrogen, prisms from 96% alcohol, m. p. 150° to 151°, giving a Hydrochloride, leaflets of m. p. 247° to 248°, $[\alpha]_D^{18} = +13°$ (water, C=5.00); Hydriodide, leaflets decomp. 195°; Picrate, decomp. 228° to 229°; Methiodide, m. p. 183° to 184°. Further ozonization of 5-desoxydihydromorphinic acid 3-methyl ester results in an amine oxide, cryst. from alcohol, decomp. 183°, $[\alpha]_D^{30} = +19.7°$ (water, p=6.34), Hydrochloride, decomp. 195° to 199°, Picrate, decomp. 196° (138). ACETYL-5-DESOXYDIHYDROMORPHINIC ACID 3-METHYL ESTER is oily; the METHIODIDE cryst. from 70% alcohol in clumps of needles decomp. 225°. CHLORO-5-DESOXYDIHYDROMORPHINIC ACID 3-METHYL ESTER, $C_{18}H_{24}O_4NCl$, from the action of PCl_5; cryst. from 96% alcohol, m. p. 143°; its PICRATE cryst. in leaflets from alcohol, decomp. 213° to 214°. 5-DESOXYDIHYDROMORPHINIC ACID 3-ETHYL ESTER (194), see page 162.

DIHYDROCODINAL is formed together with glyoxylic acid methyl- or ethyl-ester by further ozonization of ozo-dihydrocodeine or ozo-dihydroethylmorphine, also by ozonization of dihydromorphine. It was isolated in the form of its PHENYLHYDRAZONE HYDRIODIDE, $C_{21}H_{25}O_3N_3 \cdot HI$, yellow rods of decomp. p. 247°; the SEMICARBAZONE decomp. 278° (195). CHLORODIHYDROCODINAL PERCHLORATE, $C_{15}H_{18}O_3NCl \cdot HClO_4$, results from ozonization of chloro-ozo-dihydrocodeine or chlorodihydrocodide in alcoholic perchloric acid solution; it cryst. in rods containing hydrate water, sinters 165°, decomp. anhydrous at 270°; $[\alpha]_D^{20} = -19.74°$, (water, C=0.4053). The free base cryst. from 96% alcohol in orange leaflets. decomp. 206° to 207°. CHLORODIHYDRODICONAL PERCHLORATE, $C_{15}H_{20}O_4NCl \cdot HClO_4 + H_2O$, results when the ozonization of chloro-ozo-dihydrocodeine is carried out in 10% acetic acid solution, and the base isolated as perchlorate; this cryst. in double-refracting octahedra from water, decomp. 266°; $[\alpha]_D^{20} = -31.08°$ (water, C=0.3860). The same compound is obtained from ozonization of chlorodihydrocodide in 25% formic acid (195).

β-OZO-DIHYDROCODEINE is formed by the action of sodium methylate on ozo-dihydrocodeine hydrochloride; it is an oil, forming a cryst. HYDRIODIDE, $C_{18}H_{23}O_5N \cdot HI$, leaflets and needles from water, decomp. 229°; $[\alpha]_D^{20} = +52.5°$ (water, p=5.48). When treated with bromine, the base forms a DIBROMO derivative, $C_{18}H_{23}O_5NBr_2$, leaflets from 96% alcohol, sinter 170°, decomp. about 222° (138). γ-OZO-DIHYDROCODEINE, is formed from ozo-dihydrocodeine with

sodium methylate at 50°; oily, giving a cryst. HYDRIODIDE, $C_{18}H_{23}O_5N \cdot HI$, rods sintering at 215°, m. p. 219° to 220° with decomp. (138).

β-OZO-DIHYDROETHYLMORPHINE (138): Prep. by the action of cold sodium ethylate on ozo-dihydrocodeine hydrochloride; originally considered to be β-ozo-dihydrocodeine (195). Cryst. from very dilute alcohol in prisms of m. p. 170.5°, $[\alpha]_D^{18} = +24.4°$ (absol. alcohol, C=5.21). γ-OZO-DIHYDROETHYLMORPHINE (138), prep. from the β-form, or from ozo-dihydrocodeine with sodium ethylate at 50°; originally considered to be γ-ozo-dihydrocodeine (195). Cryst. from very dil. alcohol in needles, m. p. 175°, $[\alpha]_D^{18} = -8.2°$, $-7.6°$ (absol. alcohol, C=5.30, 2.64).

β-DIHYDRODICONAL is formed together with glyoxylic ester by ozonization of β- or γ-ozo-dihydroethylmorphine, or β- or γ-ozo-dihydrocodeine; isolated as the PHENYLHYDRAZONE ACETATE, $C_{21}H_{25}O_3N_3 \cdot C_2H_4O_2 + H_2O$, m. p. 205° to 206°. The OXIME ($+2H_2O$) decomp. 267° to 287°, OXIME HYDROCHLORIDE ($+H_2O$) decomp. 266°; the SEMICARBAZONE decomp. 247° (138).

CHLOROCODIZONE (260) (Ozo-α-chlorocodide) (138) see page 222.

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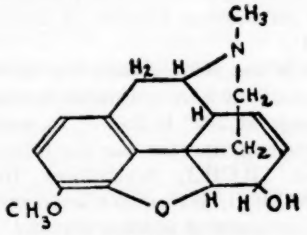
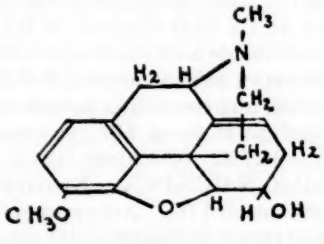
NEOPINE

The alkaloid neopine, $C_{18}H_{21}O_3N$, was isolated in the factory of T. and H. Smith & Co., Edinburgh, from the last mother liquors obtained in the separation of the alkaloids from opium. It was first described under the name "hydroxycodeine" by Dobbie and Lauder (1) in 1911.

Neopine is an isomer of codeine, from which it differs structurally only in the position of the double linkage in the hydroaromatic nucleus.



Codeine

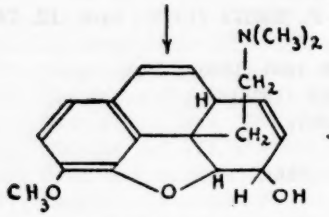


Neopine

Van Duin, Robinson, and Smith (2) were able to show that neopine adds one molecule of hydrogen to give the same dihydrocodeine as results from catalytic reduction of codeine itself. Further confirmation of the relationship between codeine and neopine was found in the results of degradation. Codeine methohydroxide, on boiling with

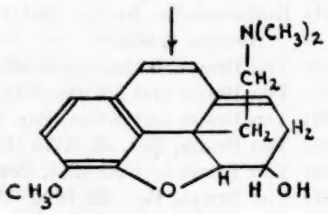
alkali, is converted nearly quantitatively to the methine base, α-methylmorphimethine. This substance isomerizes when boiled with alcoholic potassium hydroxide, to β-methylmorphimethine, a change which is generally believed to be due to a shift of the 7,8-double linkage of α-methylmorphimethine to the 8,14-position. (See p. 274.) It was found that neopine methohydroxide degrades directly to β-methylmorphimethine, a fact which indicates that the unsaturation in the hydroaromatic ring of neopine must already occupy the 8,14-position.

Codeine Methohydroxide



α-Methylmorphimethine

Neopine Methohydroxide



β-Methylmorphimethine

Descriptive Part (Neopine)

NEOPINE (B=$C_{18}H_{21}O_3N$). The base is obtained in a crystalline condition when a solution of the pure hydrobromide is treated with sufficient concentrated potassium hydroxide to produce an emulsion (the base is somewhat soluble in water) and extracted with benzene. Evaporation of the benzene leaves a varnish which can be induced to crystallize. The base is best recrystallized from ligroin of b. p. 80° to 100°; long, glistening, brittle, colorless needles, m. p. 127° to 127.5°, result. It is optically inactive in aqueous solution (C=5.1084), but on the addition of hydrochloric acid, B·HCl in 0.397 HCl, showed the value $[\alpha]_D^{25}=+18.85°$. In dry chloroform the base gives $[\alpha]_D^{23}=-28.10°$ (C=7.4740). With Fröhde's or Mandelin's reagent a yellow color changing to blue is observed. The color change is slower than in the case of codeine. An aqueous solution of the alkaloid does not immediately decolorize potassium permanganate (2). The absorption band at 1/λ 3500 observed in the spectrum of an aqueous solution of neopine hydrobromide is identical with that of codeine (1).

NEOPINE HYDROBROMIDE, B·HBr. This salt is less soluble than the hydrochloride, and crystallizes anhydrous from water in large hard prismatic crystals. It darkens at about 240°, and melts with decomp. at 282° to 283°. In water, $[\alpha]_D^{23}=+17.32°$ (C=3.696) (1) (2). NEOPINE PLATINICHLORIDE has the formula $(C_{18}H_{21}O_3N\cdot HCl)_2PtCl_4$. NEOPINE METHIODIDE, $B\cdot CH_3I$, crystallizes from methyl alcohol (1). ACETYLNEOPINE, $C_{18}H_{20}O_3NCOCH_3$, is formed when neopine is acetylated in boiling acetic anhydride in the presence of sodium acetate. It has not been obtained crystalline. It forms a methiodide which cryst. from methanol in long glistening needles, darkening at 250° and melting at 256° to 257° (corr.) with decomp. (2). DIHYDRONEOPINE is identical with dihydrocodeine (p. 197). It shows the melting points 51° to 53° and 81° to 84° like the hydrogenation product from codeine, and the form of m. p. 112° to 113° (corr.) which is obtained by crystallization from dilute methyl alcohol does not depress the melting point of the corresponding form of dihydrocodeine. NEOPINEMETHINE is identical with β-methylmorphimethine (p. 278). It was prepared from

neopine methosulphate by boiling with potassium hydroxide. It cryst. from alcohol in large twinned rhombohedral prisms of m. p. 135°. Its methiodide cryst. from water in glistening needles of m. p. 291° (decomp.) and shows the rotatory power $[\alpha]_D^{21} = +241.1°$ (absolute methyl alcohol, C=0.506), and $[\alpha]_D^{21} = +262.0°$ in 90% alcohol (C=0.3) (2).

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PORPHYROXINE

Porphyroxine, $C_{19}H_{23}O_4N$, was first obtained in a pure state by Rakshit (1) in 1919. As early as 1837 Merck (2) prepared from Bengal opium a highly colored substance to which he applied the name porphyroxine. It was however not a single substance, and Hesse (3) conjectured that it was a mixture probably containing meconidine and rhoeadine as well as other alkaloids. He noted that Merck's porphyroxine agreed in method of preparation, properties and composition with rhoeadine (4).

Rakshit's procedure for the isolation of the alkaloid from Indian opium consists in trituration of the opium with slaked lime and water, and extraction of the aqueous liquor with ether. The residue obtained from distillation of the ether is then extracted exhaustively with boiling light petroleum. The powdered residue left undissolved is triturated with dilute hydrochloric acid, filtered, and the filtrate precipitated with sodium bicarbonate. The liquid, freed of the precipitate, is extracted several times with chloroform. Evaporation of the chloroform yields porphyroxine as a brownish-yellow varnish, which crystallizes to a pink powder on rubbing. The base is purified by extraction into light petroleum (b. p. 100° to 120°) from which it crystallizes on evaporation as groups of radiating pale yellow prisms (1).

Porphyroxine melts at 134° to 135° without decomposition. It is appreciably soluble in water, and the solution reacts strongly alkaline towards cochineal, methyl orange and litmus, but does not affect phenolphthalein. The base is soluble in dilute acids, acetone, carbon disulphide, chloroform or glacial acetic acid, moderately so in benzene, carbon tetrachloride, methanol, ethanol, toluene, or ethyl acetate, only sparingly soluble in amyl alcohol, ether, light petroleum, ammonia, or barium hydroxide and almost insoluble in dilute alkali or lime water. Dilute mineral acid solutions of the base take on a porphyry color when kept exposed to air.

The pure base gives with concentrated sulphuric acid a red color; with concentrated sulphuric acid containing potassium dichromate a grass green; with concentrated nitric acid a pale yellow; and with concentrated hydrochloric acid, an orange.

In chloroform solution (C=0.508), porphyroxine shows $[\alpha]^{32} = -139.9°$.

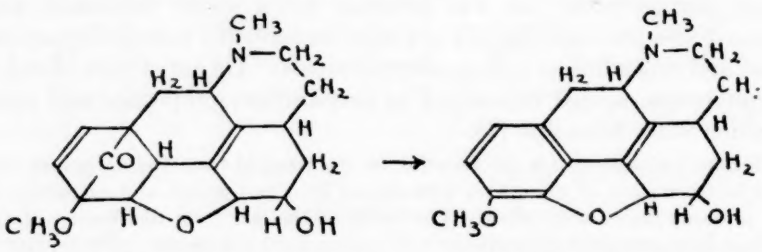
The alkaloid contains a phenanthrene nucleus (zinc dust distillation), which carries one methoxyl group. The nitrogen is tertiary

in nature. Acetylation shows the presence of one hydroxyl group, which, in view of the alkali-insolubility of the base, must be alcoholic. The property possessed by porphyroxine of forming a semicarbazone, oxime, and phenylhydrazone shows the presence of a carbonyl group (5).

The most important constitutional evidence for porphyroxine was found in its conversion to codeine through heating with 2% potassium hydroxide in the presence of hydrogen peroxide. This reaction is interpreted by Rakshit as follows:

$$C_{18}H_{23}O_3N{:}CO + KOH + H_2O_2 \longrightarrow C_{18}H_{21}O_3N + HCOOK + H_2O$$

and the carbonyl group is represented as occupying a bridge position in the codeine aromatic ring:



Porphyroxine Codeine (Pschorr Formula)

Porphyroxine itself can not be hydrogenated; its methyl ether, on the other hand, can be reduced with sodium amalgam, yielding tetrahydromethylporphyroxine; the reason for this peculiar behavior is not apparent.

In view of the relatively small amount of experimental evidence available, the structure assigned to porphyroxine can be accepted only with considerable reservation; the return to the improbable Pschorr formula (see p. 341) is particularly inacceptable.

Descriptive Part (Porphyroxine)

PORPHYROXINE ($B = C_{19}H_{23}O_4N$). —HYDROCHLORIDE, B·HCl, prismatic needles from water, softening at 140° and melting at 155°; sol. in water, chloroform, ethanol, methanol or gl. acetic acid, almost insol. in acetone, benzene, carbon tetrachloride, ethyl acetate, ether, petroleum ether, or toluene; in water, $[\alpha]^{32} = -118.8°$ (C=0.580). —PLATINICHLORIDE, $(B{\cdot}HCl)_2PtCl_4$, an ochreous cryst. powder, melting with decomp. ca. 204°. —AURICHLORIDE, unstable grayish-yellow amorph. precip. —HYDROBROMIDE, B·HBr, white needles melting at 148° to 150° to a pink liquid; $[\alpha]^{32} = -90.6°$ (water, C=0.8418). —HYDRIODIDE, B·HI, a pale brown powder which melts with decomp. at 115°; $[\alpha]^{32} = -77.8°$ (alcohol, C=0.6240). —SULPHATE, $B_2{\cdot}H_2SO_4$, pale pink radiating plates of m. p. 193° (slight decomp.); $[\alpha]^{32} = -111.4°$ (water, C=1.120). —PHOSPHATE, $B{\cdot}H_3PO_4$, a powder of m. p. 117°; $[\alpha]^{32} = -98.2°$ (water, C=1.078). —NITRATE, $B{\cdot}HNO_3$, cryst. from water in feathery tablets of m. p. 122°; $[\alpha]^{32} = -115.4°$ (water, C=1.267). —ACETATE, $B{\cdot}C_2H_4O_2$ is not crystalline. —OXALATE, $B{\cdot}C_2H_2O_4$, yellow prisms decomp. at 182°; $[\alpha]^{33} = -114.2°$ (water, C=1.868). —CITRATE,

$B_3 \cdot C_6H_6O_7$, is an amorphous powder melting at 82° to 85°; $[\alpha]^{32} = -108.6°$ (water, C=0.3190). —TARTRATE, $B_2 \cdot C_4H_6O_6$, pink cryst. powder of m. p. 116° to 118°; $[\alpha]^{32} = -95.5°$ (water, C=0.3270). —PICRATE, $B \cdot C_6H_3O_7N_3$, yellow cryst. of m. p. 198° (decomp.); $[\alpha]^{32} = -49.9°$ (water, C=0.5316).

—METHIODIDE, $B \cdot CH_3I$, amorphous hornlike mass; $[\alpha]^{25} = -82.5°$ (methanol, C=0.9000). It melts at 150° to 152°. —METHOCHLORIDE, $B \cdot CH_3Cl$, white powder melting at about 171°; $[\alpha]^{34} = -90.4°$ (water, C=0.6710). —METHOMETHYLSULPHATE, $B \cdot (CH_3)_2SO_4$, white needles from methanol, m. p. 205° (decomp.); $[\alpha]^{25} = -74.6°$ (methanol, C=0.976). —METHOHYDROXIDE, $B \cdot CH_3OH$, brown cubes from alcohol, m. p. 112° to 115° (decomp.); $[\alpha]^{34} = -71.8°$ (alcohol, C=0.508).

ACETYLPORPHYROXINE: $C_{21}H_{25}O_5N$, prep. by heating porphyroxine with acetic anhydride. It melts at 125° and shows $[\alpha]^{34} = -187.2°$ (alcohol, C=0.667). Its SULPHATE cryst. in white needles decomp. ca. 190°; $[\alpha]^{30} = -150.2°$ (water, C=0.854). Its HYDROCHLORIDE cryst. in white needles, m. p. 126°; $[\alpha]^{30} = -123.4°$ (water, C=0.857), and PLATINICHLORIDE is an orange cryst. powder m. at 230° with decomp. Its HYDROBROMIDE consists of white needles of m. p. ca. 155° (decomp.); $[\alpha]^{35} = -98.8°$ (water, C=0.9816). The HYDRIODIDE cryst. in brown needles m. p. 105° to 107° (decomp.).

PORPHYROXINE OXIME, cryst. from ether, m. p. ca. 198° with slight decomp.

PORPHYROXINE -SEMICARBAZONE, decomp. 244°. PORPHYROXINE PHENYLHYDRAZONE, cryst. from acetone, m. p. 150° with decomp.

METHYLPORPHYROXINE: $C_{20}H_{25}O_4N$, the methyl ether of porphyroxine, is prep. by heating porphyroxine methomethylsulphate with methyl alcoholic potash. It cryst. from benzol or petroleum ether in yellow needles of m. p. 125° to 126°; $[\alpha]^{28} = -131.8°$ (chloroform, C=0.5000). It yields a cryst. Hydrochloride, Hydrobromide, Sulphate, and Oxalate, but the Hydriodide, Acetate, and Phosphate are amorphous. The Platinichloride cryst. in orange needles. The base can not be acetylated. Its Oxime cryst. from methanol and melts at 185° to 186°, the Semicarbazone m. at 217° (decomp.), the Phenylhydrazone is amorphous, m. p. 189° (decomp.).

METHYLTETRAHYDROPORPHYROXINE: $C_{20}H_{29}O_4N$, is prep. by reduction of porphyroxine methomethylsulphate in dil. sulphuric acid with sodium amalgam. It cryst. from benzol or methyl alcohol in white plates of m. p. 150°. Its solutions in mineral acids become deep red on exposure to air. The base forms a cryst. Hydrochloride, Hydrobromide, Hydriodide, Nitrate, Acetate, and Platinichloride. The Aurichloride is amorphous and unstable. The base can not be acetylated. It forms an Oxime of m. p. 234° to 235°, a Semicarbazone which decomp. ca. 210°, and a Phenylhydrazone of m. p. 126°.

Bibliography (Porphyroxine)

(1) Rakshit, J. Chem. Soc. **115,** 455 (1919).
(2) Merck, Ann. **21,** 201 (1837).
(3) Hesse, Ann. **153,** 47 (1870).
(4) Hesse, Ann. suppl. **4,** 50 (1864–65).
(5) Rakshit, Ber. **59,** 2473 (1926).

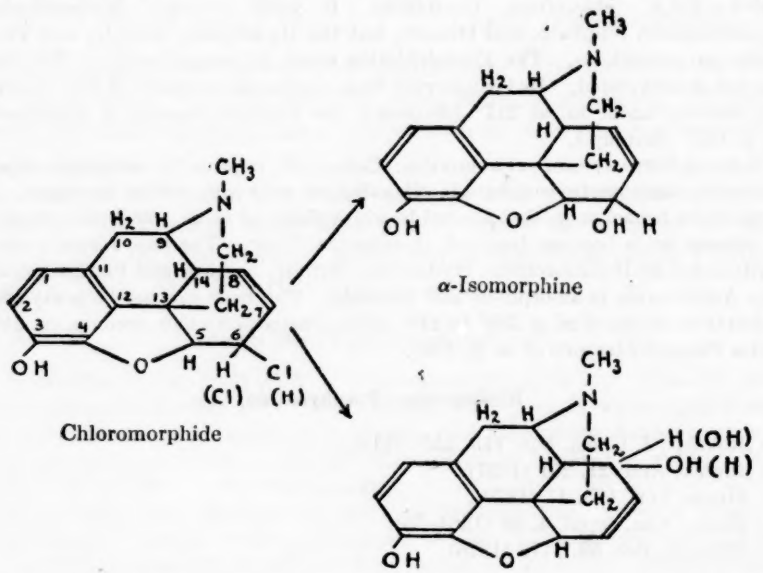
THE HALOGENO-MORPHIDES AND -CODIDES—THE ISOMERS OF MORPHINE AND CODEINE

The alcoholic hydroxyl group of morphine or codeine may be replaced easily by chlorine or bromine by the action of such agents as thionyl chloride and the phosphorous halides. The products are

designated as halogenomorphides and halogenocodides, respectively. The chloro derivatives ordinarily obtained have been named α-chloromorphide and α-chlorocodide. These undergo a rearrangement under suitable conditions to the isomeric compounds, β-chloromorphide and β-chlorocodide, which are believed to differ from the α-forms only in the configuration of H- and Cl- on the asymmetric carbon atom.

Hydrolysis of the halogenomorphides results in replacement of halogen on the asymmetric carbon atom by hydroxyl. As the investigations of Walden have shown, such replacement may be expected to lead to configurational changes; in the case of the halogenomorphides the relationships are further complicated by structural changes. Hydrolysis yields three isomers of morphine: α-isomorphine represents a stereoisomer of morphine, differing from it by the configuration of H- and -OH on C-6; β- and γ-isomorphine are stereoisomers, carrying the hydroxyl group on C-8, and are therefore structural isomers of morphine and α-isomorphine.

The hydrolysis of the halogenocodides runs parallel to that of the morphides. Isocodeine, a stereoisomer of codeine, is obtained, and two structural isomers of codeine, named pseudocodeine and allopseudocodeine, which constitute a stereoisomeric pair with the -OH group on C-8.

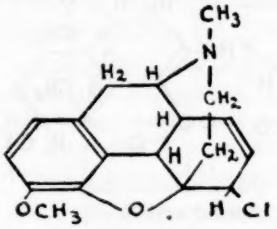


Since nearly all of the conclusions concerning the halogenomorphides and isomeric morphines are based upon experiments in the codeine series, the chemistry and relationships of chlorocodide and the isomeric codeines will be considered first.

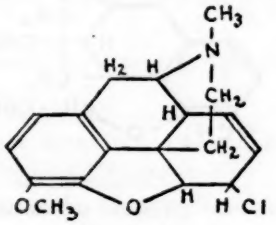
The Halogenocodides

Matthiessen and Wright (1) first observed the formation of a chlorocodide, from treatment of codeine with hydrochloric acid at 100° (*cf.* Göhlich (2) Knorr and Hörlein (3)). They analyzed the base and its salts, and showed that it could be converted to apomorphine, or back to codeine (probably one of the isomers of codeine (4)).

α-Chlorocodide is prepared by treatment of codeine with phosphorous pentachloride (5) (6), phosphorous trichloride (7), or thionyl chloride (8). It likewise results from the action of these agents on pseudocodeine (9) (10), or from methylation of α-chloromorphide (7).



Chlorocodide
(Knorr-Wieland)



Chlorocodide
(Gulland and Robinson)

The halogen in α-chlorocodide is comparatively active; its removal by hydrolysis is considered below. Reduction with zinc and alcohol results in loss of hydrochloric acid and reductive scission of the ether ring, with formation of the phenolic desoxycodeine-A (3) (11) (63) (p. 235). When the reduction is accomplished with sodium and alcohol (11) (64), dihydrodesoxycodeine-A results, which was erroneously believed by Freund (6) to be a tetrahydrodesoxycodeine (α). Catalytic hydrogenation of α-chlorocodide gives a dimolecular reduction product, or a tetrahydrodesoxycodeine, according to the conditions (36). (See p. 240.) Alkyl magnesium halides likewise react with α-chlorocodide to reduce it to desoxycodeine (63).

Attempts to convert α-chlorocodide into codeine methyl ether by the action of sodium methylate were unsuccessful (12) (13). Drastic treatment in the autoclave (14) gave a product which proved to be the methyl ether of pseudocodeine (16) (17). Knorr and Hartmann (16) found, in fact, that simply heating α-chlorocodide to 110° with an alcohol or phenol resulted in formation of the corresponding ether of the pseudocodeine series.

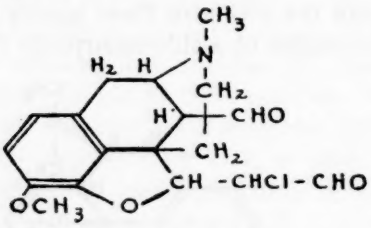
α-Chlorocodide reacts with potassium iodide in boiling alcohol to form an iodocodide (18) (63).

By treatment of α-chlorocodide with amines, the halogen may be replaced by an amino group. Von Braun and Kindler (19) prepared dimethylaminocodide and diethylaminocodide in this way (*cf.* diethylaminomorphide (8)).

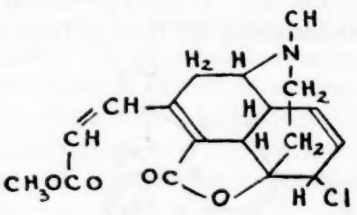
Degradation of α-chlorocodide methiodide by the Hofmann method failed; the methohydroxide, on warming, gives a solution containing chlorine ion, suggested as coming from an apocodeine methochloride (12).

The action of an excess of phosphorous pentachloride on codeine at 70° results in a dichloro compound (5); see chlorocodeine, page 194.

Treatment of α-chlorocodide with ozone yields chlorocodizone (ozo-α-chlorocodide), which contains two more oxygen atoms than chlorocodide. Wieland and Small (20) interpreted this as a scission of the 7, 8-double linkage of α-chlorocodide; Speyer and Roell (21) have advanced evidence to show that the aromatic ring has been opened:

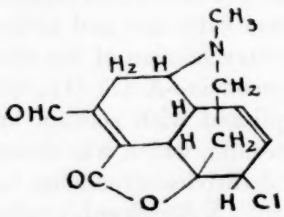


Chlorocodizone
(Wieland and Small)

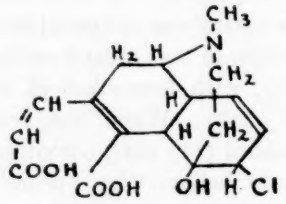


Ozo-α-chlorocodide
(Speyer and Roell)

By further ozonization of chlorocodizone, Speyer obtained the aldehyde, α-chlorocodinal; the hydrolytic action of boiling dilute sulphuric acid yielded an amino-acid, α-chloromorphinic acid:



α-Chlorocodinal



α-Chloromorphinic Acid

The chlorine atom of chlorocodizone is easily removed by reduction with zinc and acetic acid, giving desoxycodizone. With alcoholic potassium hydroxide, loss of hydrochloric acid takes place (anhydrocodizone), and a portion of the material suffers a loss of the ethanamine side chain as well, forming two nitrogen-free isomeric substances (20).

When α-chlorocodide is heated with concentrated hydrochloric acid (3), or is heated above its melting point (22), preferably in an indifferent solvent (9), it is converted to the isomeric β-chlorocodide. This base has also been obtained from codeine or pseudocodeine, by heating with concentrated hydrochloric acid (3); as Speyer (9) points out, however, it is not improbable that the primary product here is the α-isomer, which is transformed to the β-form by the hot hydrochloric acid. With thionyl chloride, which is not known to cause conversion of the α- to the β-form, codeine and pseudocodeine give exclusively α-chlorocodide, while isocodeine and allopseudocodeine give only β-chlorocodide (9).

β-Chlorocodide is the methyl ether of β-chloromorphide, from which it is formed by the action of diazomethane (3). α- and β-chlorocodide are believed to differ only in the spatial arrangement of the chlorine and hydrogen on C-6; no strict proof of this has ever been advanced.*

Reduction of β-chlorocodide with zinc and alcohol gives the same desoxycodeine as is obtained from α-chlorocodide (3) (11). By catalytic reduction of β-chlorocodide (believed at the time to be allopseudochlorocodide) Speyer and Krauss (23) arrived directly at a compound claimed to be α-tetrahydrodesoxycodeine. (See Small and Cohen (64).) Mannich (24), on the other hand, obtained two products, one of which is tetrahydrodesoxycodeine, the other a nonphenolic dihydrodesoxycodeine (p. 289).

β-Chlorocodide is converted by concentrated hydrochloric acid at 150° into apomorphine hydrochloride and methyl chloride (1).

With ozone, β-chlorocodide yields an oily ozo-β-chlorocodide (21).

By treatment of α- or β-chlorocodide with ethyl mercaptan, Pschorr and Rollett (22) prepared the ethylthiocodides, four isomeric substances (p. 229).

A third chlorocodide, resulting from treatment of pseudocodeine with phosphorous pentachloride, has been described (10) (25); pseudochlorocodide is not crystalline, and was characterized as the methiodide. With thionyl chloride and pseudocodeine Speyer and Rosenfeld (9) obtained exclusively α-chlorocodide. Like the α- and β-isomers, pseudochlorocodide reduces to desoxycodeine.

Tetrahydropseudochlorocodide, from tetrahydropseudocodeine and phosphorous pentachloride, reduces with sodium and alcohol to a compound (23) thought to be identical with the so-called α-tetrahydrodesoxycodeine of Freund.

A supposed allopseudochlorocodide (23), from allopseudocodeine, proved to be identical with β-chlorocodide (9).

The halogen in the chlorocodides is hydrolyzed out quite readily when they are heated with water (1) (2) or dilute acids (3) (22) (26) (27). Three isomers of codeine result, in approximately the proportions given (4):

	isocodeine	pseudocodeine	allopseudocodeine
α-chlorocodide	25%	45%	15%
β-chlorocodide	55%	10%	20%

Göhlich (2) states that he obtained codeine itself by hydrolysis of α-chlorocodide.

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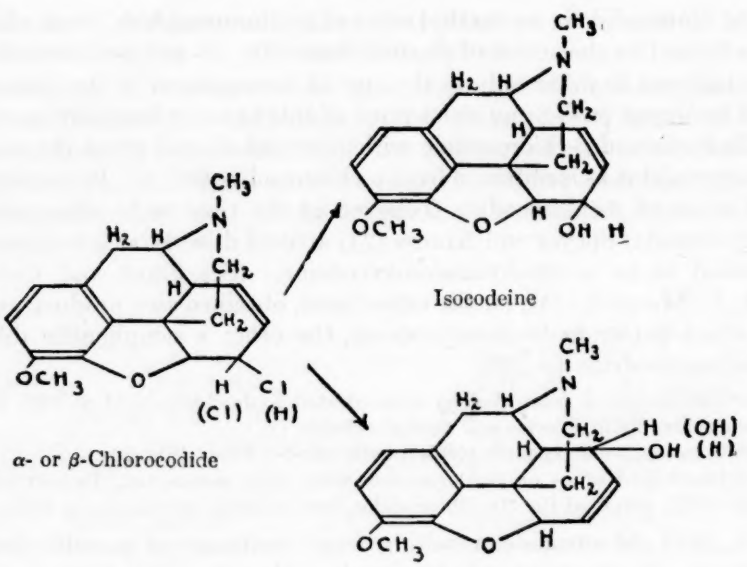
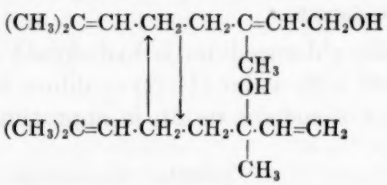
* See Appendix, p. 362.



Evidence which will be presented in the discussion of the isomeric codeines below shows that in isocodeine the hydroxyl group unquestionably is on C-6, in pseudocodeine and allopseudocodeine on C-8. The formation of the latter two substances involves a structural change, for which Gulland and Robinson (28) (29) find an analogy in the interconvertibility of geraniol and linalool,



where the shift takes place during reactions quite similar to the hydrolysis of the halogenocodides.

The formation of halogen-free isomeric bases through hydrolysis of the chloro compounds is not limited to codeine and morphine. Pschorr and Dickhäuser (30) found that in the methylmorphimethine series, the corresponding chloro derivative, chloro-α-methylmorphimethine, could be hydrolyzed with dilute acids to γ-, δ-, and ε-methylmorphimethine. γ- and δ-methylmorphimethine correspond to isocodeine, and ε-methylmorphimethine corresponds to pseudocodeine. (See p. 273.)

While the double bond in the chlorocodides can not be reduced without loss of the halogen, a chlorodihydrocodide may be prepared from dihydrocodeine with phosphorous pentachloride (24); it is known in only one form. The chlorine is not as active as in the chlorocodides, and can not be hydrolyzed out to give dihydrocodeine

isomers, as might be expected (9). Electrolytic reduction (6) yields the dihydrodesoxycodeine-C (64) of m. p. 111° (p. 239).

Chlorodihydrocodide is very stable toward acid or alkali; with hydriodic acid it goes to chlorodihydromorphide (24). Treatment of chlorodihydrocodide with sodium methylate at 140° results in splitting out hydrogen chloride; the product is the nonphenolic desoxycodeine-C, which probably possesses a structure like that of pseudocodeine, with the unsaturation at C-6 to C-7 (63). (*Cf.* Knoll and Co. (65), Mannich and Löwenheim (24).)

Ozonization of chlorodihydrocodide results in splitting of the aromatic ring, with formation of chlorodihydrocodinal, or chlorodihydrodiconal, according to the conditions (31). (See p. 199.)

Chlorodihydrocodide methiodide has been degraded to des-N-methylchlorodihydrocodide; the nitrogen-free end product could not be isolated. The above des-base can be reduced catalytically to a dihydro derivative (6), which is apparently identical with the chlorotetrahydro-α-methylmorphimethine formed by the action of phosphorous pentachloride on tetrahydro-α-methylmorphimethine (32) (p. 272).

All attempts to prepare a second chlorodihydrocodide from dihydroisocodeine failed; phosphorous pentachloride or thionyl chloride yielded only compounds containing phosphorus or sulphur, respectively (36).

Bromocodide (7) (27), which resembles the chlorocodides, is known in but one form; attempts to rearrange this to an isomer failed (22). It yields on hydrolysis principally isocodeine, together with a small amount of pseudo- and allopseudocodeine (7) (27) (33) (34). These facts indicate that it corresponds to β-chlorocodide. (*Cf.* Faltis (35), Pschorr (22).)

Iodocodide is formed when α-chlorocodide is heated with potassium iodide in methyl or ethyl alcohol (18). β-chlorocodide does not react under these conditions (63). Iodocodide hydrolyzes like the chlorocodides (18); when shaken with silver chloride in dilute alcohol, it is converted to α-chlorocodide (63).

The Isomers of Codeine

Isocodeine, as indicated above, is the chief product resulting from the hydrolysis of β-chlorocodide (3) (7), or bromocodide (7) (27) (34); it forms only about 25% of the hydrolysis products from α-chlorocodide (4). It is the methyl ether of α-isomorphine, from which it may be prepared by methylation (7) (27).

Isocodeine differs from codeine solely in the configuration of the hydrogen and hydroxyl on the asymmetric 6-carbon atom; Knorr and Hörlein (37) were able to show that on oxidation at C-6 the isomerism disappeared, and the same codeinone was formed from both. The structure of codeinone depends upon its degradation to 3,4,6-trimethoxyphenanthrene (38) (p. 248).

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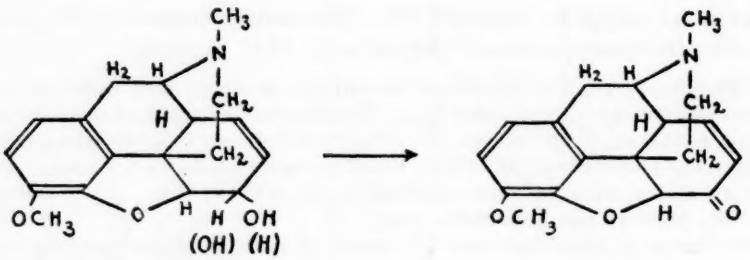


Codeine, Isocodeine — Codeinone

Isocodeine is converted by thionyl chloride to β-chlorocodide in nearly quantitative yield (9).

The acetoacetyl derivatives of the isomers of codeine were investigated by Knorr and coworkers (58).

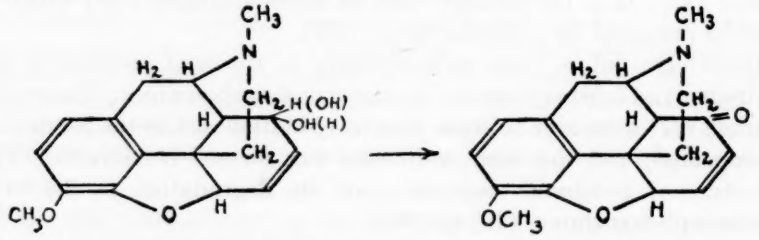
Through catalytic reduction of isocodeine a dihydroisocodeine is obtained by saturation of the double linkage (39); the ether bridge is intact. By exhaustive methylation dihydroisocodeine gives a nitrogen-free product which is isomeric with that obtained from dihydrocodeine (23).

Isocodeine methiodide degrades to γ-methylmorphimethine (p. 275) (27) (40) and finally to methylmorphenol. Similarly, isocodeine methyl ether methiodide, which is prepared by methylation in alkaline solution with dimethyl sulphate followed by precipitation with potassium iodide, yields γ-methylmorphimethine methyl ether (17).

An isocodeine from the hydrolysis of dihydrothebaine was briefly described by Freund in 1899 (41); it has never been further studied.

Like isocodeine, pseudocodeine [80] is found among the hydrolysis products of the halogenocodides (10) (13) (26). It was prepared originally in an amorphous condition by Anderson (42) and Armstrong (43), later crystalline by Merck (44) and Göhlich (2). It is the methyl ether of γ-isomorphine (7) (40).

Pseudocodeine still contains the codeine ring system, for it is easily converted back to α- or β-chlorocodide,[81] and its chloro derivative, chloropseudocodide, gives the same desoxycodeine as is derived from codeine itself. By oxidation of pseudocodeine, pseudocodeinone is obtained, in which the carbonyl group has the 8-position (see p. 251) (25) (45); pseudocodeine therefore has the hydroxyl at this point and is a structural isomer of codeine and isocodeine.

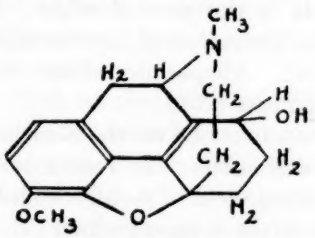


Pseudo-, Allopseudocodeine — Pseudocodeinone

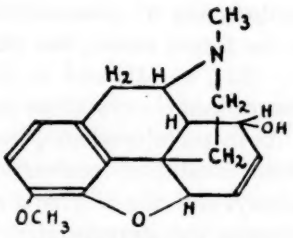
[80] The name "pseudocodeine" is illogical for this substance, since it in no way corresponds to pseudomorphine. For this reason, Lees (7) proposed "neoisocodeine," which, however, has never come into general usage.

[81] *Cf.* Pschorr, Ber. 45, 2214 (footnote) (1912).

To prove that the wandering of the hydroxyl from C-6 to C-8 takes place in the change codeine ——→pseudocodeine, and not during the conversion of pseudocodeine to pseudocodeinone, Pschorr (46) carried through the degradation of pseudocodeine methyl ether, and obtained as end product 3, 4, 8-trimethoxyphenanthrene; degradation of the corresponding codeine methyl ether gave 3, 4, 6-trimethoxyphenanthrene.



I. Pseudocodeine
(Pschorr, 1909) (46)



II. Pseudocodeine
(Gulland and Robinson, 1925) (28)

When codeine is melted with oxalic acid, the primary product is pseudocodeine (Beckett and Wright's "dicodeine") (47); this is further converted in the reaction to pseudoapocodeine, which is obtained in better yields by starting with pseudocodeine and oxalic acid. Pseudoapocodeine is believed to be the 3-methyl ether of apomorphine (48).

Pseudocodeine, with concentrated hydrochloric acid, gives β-chlorocodide (3), probably as a rearrangement product from the primarily formed α-chlorocodide. With thionyl chloride, only α-chlorocodide is obtained (9). Using phosphorous pentachloride, Knorr found, along with about 25% α-form, a chloropseudocodide (10) (25).

Pseudocodeine methiodide, subjected to exhaustive methylation, goes to ϵ-methylmorphimethine (10) (33) (40) (49) (p. 217), which degrades to morphenol (10). Since ϵ-methylmorphimethine does not rearrange to an isomer (which in the case of the α- and γ-methylmorphimethines was believed to take place through a shift of the double bond from 8,14 to 14,13) the double linkage was assigned the 14, 13-position in pseudocodeine (10) (Formula I above). The 6,7-double bond (Formula II) accounts equally well for the behavior of pseudocodeine.

The formation of pseudocodeine ethers by reaction of α-chlorocodide and sodium methylate or alcohols has already been mentioned; these ethers are also obtained (in the form of their quaternary alkylates) from pseudocodeine with dimethyl sulphate and alkali (17). Treatment of the ethers with cyanogen bromide results in a series of norcyano derivatives (50).

Nitropseudocodeine results from the action of nitric acid; it is different from nitrocodeine, but oxidizes to the same nitrocodeic acid (51).

The catalytic reduction of pseudocodeine takes place with reduction of the double bond and opening of the ether bridge to a phenol, tetrahydropseudocodeine (39). Sodium and alcohol, or electrolytic methods, give the phenolic dihydropseudocodeine, which with catalytic hydrogen goes to the same tetrahydro derivative (23).

The N-oxide derivatives of pseudocodeine have been investigated by Speyer and coworkers (23) (52). Unlike codeine, pseudocodeine does not yield a dihydroxy compound on treatment with permanganate (53), but is left largely unattacked.

The stereoisomer of pseudocodeine is allopseudocodeine (at first called β-isocodeine). This was first prepared by Lees (7) (54) by methylation of β-isomorphine of which it is the methyl ether. It is also found among the products from the hydrolysis of bromocodide (7) (33), α- (4), and β-chlorodides (3) (4). Allopseudocodeine was first obtained crystalline by Speyer and Krauss (23).

As in pseudocodeine, the hydroxyl group must be on the 8-carbon atom; oxidation converts it to pseudocodeinone. It reacts with thionyl chloride to give a nearly quantitative yield of β-chlorocodide, whereas the stereoisomer, pseudocodeine, gives α-chlorocodide (9).

On catalytic reduction, allopseudocodeine takes up 2 molecules of hydrogen, saturating the double bond and opening the oxygen bridge to the phenolic tetrahydroallopseudocodeine (23). Isolation of a nitrogen-free product by exhaustive methylation of the tetrahydro compound failed. The double compound (m. p. 147.5°) of allopseudocodeine and isocodeine described by Lees (7) gives on reduction equal amounts of dihydroisocodeine and tetrahydroallopseudocodeine, which are separated through the solubility of tetrahydroallopseudocodeine in alkali.

Exhaustive methylation of allopseudocodeine yields ξ-methylmorphimethine (33) (p. 275).

Neopine, which constitutes a fifth codeine, is considered in a separate section (p. 205).

The properties of the isomeric codeines are summarized in the following table:

	m. p.	$[\alpha]_D$	Hydriodide		Methiodide		Methylmorphimethine
			m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	
	Degrees		*Degrees*	*Degrees*	*Degrees*	*Degrees*	
Codeine	155	−135° $CHCl_3$			273	−79	α
Isocodeine	171–172	−150.6° EtOH			265	−102.1	γ
Pseudocodeine	181–182	−96.6° EtOH	260–265	−57	278	−50.6	ε
Allopseudocodeine	116–117	−235.4°	280–285	−152	215	−142	ξ

Halogenocodides

Base	m. p.	$[\alpha]_D$	Methiodide	
			m. p.	$[\alpha]_D$
		Degrees	*Degrees*	*Degrees*
α-Chlorocodide	147°, 152°–153°	−380	168	−215
β-Chlorocodide	152°–153°, 156°–157°	−10	160–180	+4.6
Chloropseudocodide	oil		185–186	−229
Bromocodide	161°–162°	+48.6		
Iodocodide	decomp. ca. 200°	+136.5	188	

The Halogenomorphides

Corresponding to the α- and β-forms of chlorocodide, two chloromorphides are known. α-Chloromorphide is prepared from morphine by treatment with phosphorous trichloride (40) (55), thionyl chloride (8), or dry liquid hydrogen chloride (56). It has the properties of a phenol, and permits the introduction of only one acetyl group on acetylation; the alcoholic hydroxyl group has been replaced by chlorine.

With methylating agents, α-chloromorphide yields α-chlorocodide (7). It is converted by concentrated hydrochloric acid to the isomer, β-chloromorphide (57), which in turn methylates to β-chlorocodide. The relation of the isomeric chloromorphides to the chlorocodides is thus clearly established, and the isomerism of α- and β-chloromorphide must be of the same nature as that of α- and β-chlorocodide.

Attempts to split out hydrochloric acid from α-chloromorphide with such reagents as sodium acetate, sodium carbonate, or amines, to arrive at an isomer of apomorphine have failed. Amines combine with it, but can not again be split off (8). Treatment with potassium hydrosulphide gives a dimolecular product, bis-thiomorphide (56); the action of ethyl mercaptan gives isomeric ethyl thiomorphides (59), analogous to the ethyl thiocodides (p. 228).

Reduction of α-chloromorphide with tin and acid results in desoxymorphine, a substance of unknown structure (55). Catalytic reduction of α-chloromorphide (palladium on barium sulphate) yields a dihydrodesoxymorphine, which methylates to the nonphenolic dihydrodesoxycodeine-D (61) (p. 239).

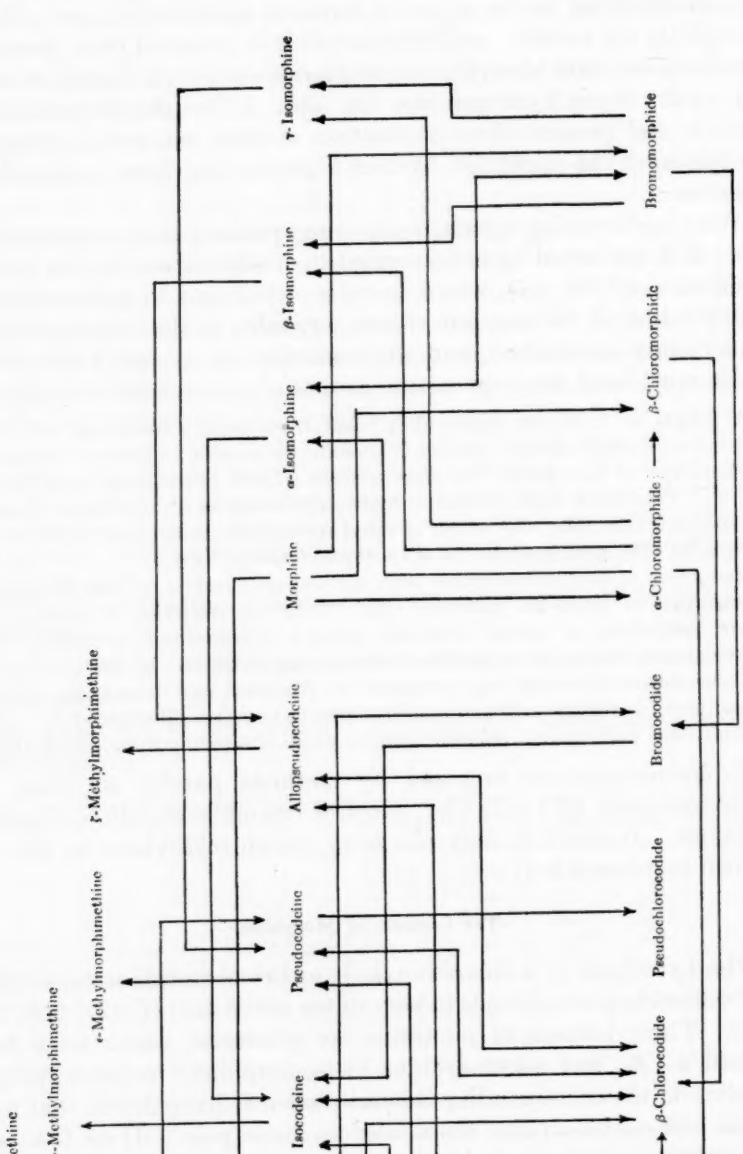
Chlorodihydromorphide was prepared by Mannich and Löwenheim (24) by the action of hydriodic acid and red phosphorous on chlorodihydrocodide. Dihydromorphine with thionyl chloride likewise yields chlorodihydromorphide (62).

Bromomorphide is prepared by methods parallel to those for chloromorphide (27) (55) (56), which it resembles closely in chemical behavior. It exists in only one form, which methylates to the one known bromocodide (7).

The Isomers of Morphine

The hydrolysis of α-chloromorphide or bromomorphide takes place on boiling these compounds in very dilute acetic acid (7) (27) (40) (54) (55). Three isomers of morphine are produced, which have been named α-, β-, and γ-isomorphine (γ-isomorphine = neoisomorphine). Studies on the corresponding isomeric codeines have shown that morphine and α-isomorphine are a stereoisomeric pair (OH on C-6) and are structural isomers of the stereoisomeric pair (OH on C-8) β- and γ-isomorphine.

α-Isomorphine corresponds to isocodeine, since it methylates to this. Phosphorous tribromide converts it to bromomorphide, whereas phosphorous trichloride gives a noncrystalline derivative (27). Exhaustive methylation of α-isomorphine leads through isocodeine methiodide and γ-methylmorphimethine to the same morphenol methyl ether as is obtained from morphine (27).


α-Methylmorphimethine
γ-Methylmorphimethine
ε-Methylmorphimethine
ζ-Methylmorphimethine
Codeine
Isocodeine
Pseudocodeine
Allopseudocodeine
Morphine
α-Isomorphine
β-Isomorphine
γ-Isomorphine
α-Chlorocodide
β-Chlorocodide
Pseudochlorocodide
Bromocodide
α-Chloromorphide
β-Chloromorphide
Bromomorphide

In contrast to morphine, α-isomorphine does not readily reduce gold chloride (27).

Degradation of α-isomorphine methiodide with acetic anhydride gives acetyldihydroxyphenanthrene, as does morphine methiodide (27).

β-Isomorphine is formed in relatively small amounts in the hydrolysis of the halogenomorphides (27) (40). Its methyl ether is allopseudocodeine (33) (β-isocodeine (7)). The behavior with phosphorous halides has not been investigated.

γ-Isomorphine was the last of the isomeric morphines to be isolated, although it forms the chief product of the hydrolysis (7) (40) (54). Methylation results in pseudocodeine; the Hofmann degradation leads to ε-methylmorphimethine (33) (40). Other reactions of γ-isomorphine have not been studied.

The properties of the isomeric morphines and their important derivatives are summarized for comparison:

Base	m. p.	$[\alpha]_D$	Hydrochloride		Methiodide		Methyl ether
			m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	
	Degrees	*Degrees*	*Degrees*	*Degrees*	*Degrees*	*Degrees*	
Morphine	254	−130.9	200	−111.5	286	−72.9	Codeine.
α-Isomorphine	251	−167	.....	−150	276	−91.5	Isocodeine.
β-Isomorphine	182	−216.2	.....	−200.8	250	−146.1	Allopseudocodeine.
γ-Isomorphine	278	−94	314	−76	293	−50	Pseudocodeine.

The halogenomorphides

Base	m. p.	$[\alpha]_D$	Hydrochloride		Hydrobromide		Methiodide	
			m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
	Degrees	*Degrees*		*Degrees*	*Degrees*	*Degrees*	*Degrees*	
α-Chloromorphide	192 (204)	−375.2	.....	−315.3	.....	−268.6	207	.....
β-Chloromorphide	188	−5	.....	.....	.....	.....	210	.....
Bromomorphide	170	+68	.....	+41.1	196	+39.5	200	.....

Descriptive Part (The Halogeno-Morphides and -Codides—The Isomers of Morphine and Codeine)

α-CHLOROCODIDE ($B=C_{18}H_{20}O_2NCl$) (1) (5), prep. from codeine with PCl_5, (5) (6) (22) or $SOCl_2$ (8). 80 g. of codeine (dried at 110°) is added with cooling and stirring to the solution of 90 g. PCl_5 in 300 c. c. $CHCl_3$. After 24 hours at room temp., pour into 1.5 to 2.1 ether, and separate the oily hydrochloride. This is warmed with soda solution until no longer violet, and the now cryst. chlorocodide rubbed with cold alcohol to remove tars. It is best recryst. from ligroin; yield, 60 to 65 g. (6). The yield may be increased up to 90% to 95% if the PCl_5 is allowed to act on the codeine for only 2 hours (63). Colorless leaflets or glassy prisms of m. p. 147° to 148° (5) (9) (152° to 153° (7)); mod. sol. in alcohol, ether, benzene, sparingly in ligroin, insol. in water or alkalies. $[\alpha]_D=-381.2°$ ($CHCl_3$, C=0.9820) (7). Prep. from α-chloromorphide, Lees (7). Hydrolysis, Knorr (4); reduction, Knorr (11), Freund (6), Mannich (24); Small

(63) (64); action of ozone, Wieland (20), Speyer (21). —HYDROCHLORIDE, viscous sirup (5). —PLATINICHLORIDE $(B{\cdot}HCl)_2PtCl_4$, brown-yellow ppt. —ACID TARTRATE, white needles from water, m. p. 198° to 200°, $[\alpha]_D^{27.5} = -218.7°$ (water, C=1.856) (63). —METHIODIDE (prep. in cold acetone) m. p. 168°, $[\alpha]_D^{15} = -215°$ (10) (56). BROMOCHLOROCODIDE (5), from bromocodeine with PCl_5, prisms from ligroin, m. p. 131°.

DICHLOROCODIDE (5), from codeine heated with excess of PCl_5, $C_{18}H_{19}O_2NCl_2$, prisms from alcohol, m. p. 196° to 197°, giving a Hydrochloride, decomp. 160° to 170°, and a cryst. Platinichloride. Chlorocodeine with PCl_5 yields an isomeric compound.

PIPERIDOCODIDE (13): $C_{23}H_{30}O_2N_2$, from chlorocodide and piperidine; m. p. 118°, forms a Dihydrochloride, a Monomethiodide, m. p. 256° and a Dimethiodide of m. p. 250°.

α-CHLOROCYANONORCODIDE (50) (60): $C_{18}H_{17}O_2N_2Cl$, from BrCN on α-chlorocodide, or $SOCl_2$ on cyanonorcodeine; m. p. 187° to 188°, $[\alpha]_D^{20} = -390°$ ($CHCl_3$, C=2.0). It forms a Diethylamino deriv. m. 187° to 188° whose Platinichloride decomp. 248° to 250°.

CHLOROCODIZONE (20), (ozo-α-chlorocodide) (21): $C_{18}H_{20}O_4NCl$, prep. by ozonization of the neutral solution of α-chlorocodide in dil. HCl. Cryst. from 70° ligroin, m. p. 104°, $[\alpha]_D^{22} = -231°$ (alcohol, p=3.13). —HYDROCHLORIDE, needles decomp. 213°. —HYDROBROMIDE, decomp. 201°. —HYDRIODIDE, sinters 160°, decomp. 174°. —PICRATE, m. p. 171°.

DESOXYCODIZONE: $C_{18}H_{21}O_4N$, from reduction of chlorocodizone with zinc-dust and acetic acid; m. p. 161°. The HYDROCHLORIDE, cryst. from methyl alcohol, m. p. 223° to 224° (decomp.) (20).

ANHYDROCODIZONE: $C_{18}H_{19}O_4N$, from treatment of chlorocodizone with methyl alcoholic potassium hydroxide, yellow needles, m. p. 110°; accompanied by yellow plates, m. p. 140° to 142°, of unknown nature. In the same reaction, isomeric nitrogen-free products, $C_{15}H_{12}O_4$, appear, m. p. 88° and 159°; the 159° substance gives a methyl ether of m. p. 105° to 108°. With potassium acetate, chlorocodizone yields the compound $C_{18}H_{19}O_2N$, m. p. 189° (20).

α-CHLOROCODINAL is obtained when chlorocodizone is further ozonized; isolated as the amorphous phenylhydrazone, $C_{21}H_{22}O_2N_3Cl$ (21).

α-CHLOROMORPHINIC ACID: $C_{17}H_{20}O_5NCl + H_2O$, results from boiling chlorocodizone with 15% sulphuric acid; leaflets from methanol, decomp. 192° (21).

6-DESOXYDIHYDROMORPHINIC ACID 3-METHYL ESTER, from reduction of chlorocodizone hydrochloride with hydrogen and palladium black; isolated as the cryst. PICRATE, leaflets sintering 170°, m. 200° to 205°, decomp. 221° (21).

β-CHLOROCODIDE: (B=$C_{18}H_{20}O_2NCl$) (3), prep. by heating α-chlorocodide (9) (22), from codeine, pseudocodeine, or α-chlorocodide, with hot conc. HCl (3) or from allopseudocodeine or isocodeine with $SOCl_2$ (9). A solution of α-chlorocodide in bromobenzene was refluxed for one hour, extracted cold with dil. HCl, and the extract treated with ammonia and ether. Yield, 70% to 75% (9). Prep. from β-chloromorphide with diazomethane, Knorr (3). Cryst. from alcohol in scales, from ether in right-angled leaflets, m. p. 152° to 153° (156° to 157° (22)); $[\alpha]_D^{15} = -10°$ (−12°) (absol. alcohol, C=1.0). Hydrolysis, Knorr (3) (4); reduction, Knorr (3) (11), Speyer (23), Mannich and Löwenheim (24). —HYDROCHLORIDE (61), cryst. from water, alcohol, or acetone, sinters 162°, melts at 168° to 171°; $[\alpha]_D^{30} = -3.85°$ (methanol, C=2.335). —ACID TARTRATE white cryst. from water m. p. 190° to 192°; $[\alpha]_D^{20} = +8.3°$ (water, C=1.683) (63). —METHIODIDE (10), cryst. from methyl alcohol, m. p. indefinite, $[\alpha]_D^{15} = +4.6°$ (25% alcohol).

β-CHLOROCYANONORCODIDE: (50) (60), $C_{18}H_{17}O_2N_2Cl$, m. p. 197° to 198°, $[\alpha]_D^{20} = -97.5°$ ($CHCl_3$, C=2.0).

OZO-β-CHLOROCODIDE is obtained as an oil, from ozonizing β-chlorocodide; the PICRATE, $C_{18}H_{20}O_4NCl \cdot C_6H_2(NO_2)_3OH$ cryst. in needles from gl. acetic acid, decomp. 217° (21).

CHLOROPSEUDOCODIDE: (B=$C_{18}H_{20}O_2NCl$), prep. from pseudocodeine with PCl_5; noncrystalline, isolated as the unstable METHIODIDE, m. p. 185° to 186°, $[\alpha]_D^{15} = -227.4°$, −229°, (in 25% alcohol, C=0.51, 0.985) (10) (25).

TETRAHYDROCHLOROPSEUDOCODIDE: $C_{18}H_{24}O_2NCl$, from PCl_5 on tetrahydropseudocodeine, leaflets from dil. alc., m. p. 103°. Reduction with Na and alcohol Speyer (23). (*Cf.* Small (64).)

BROMOCODIDE: (B=$C_{18}H_{20}O_2NBr$), prep. in nearly quant. yield from codeine with PBr_3 in chloroform solution. Recryst. from alcohol, pearly scales m. p. 162°. $[\alpha]_D^{20} = +56.5°$ (alcohol, C=1.887) (27). The product obtained by methylation of bromomorphide has $[\alpha]_D^{20} = +48.6°$ (7). Prep. from pseudocodeine, Knorr (10); hydrolysis, Lees, etc. (7) (27) (34), Knorr (33); reaction with potassium hydrosulphide, Pschorr (56), ethyl mercaptan (22).

IODOCODIDE (18): (B=$C_{18}H_{20}O_2NI$), prep. by refluxing α-chlorocodide with potassium iodide in methanol; cryst. in white monoclinic prisms or needles from benzene-ligroin or methanol. It melts at 159° to 160°; it is sol. in $CHCl_3$ or benzene, sparingly sol. in ethyl acetate, methanol or ether; $[\alpha]_D^{22} = +136.5°$ ($CHCl_3$ C=2.62) (63). Hydrolysis, conversion to desoxycodeine-A, or to α-chlorocodide, Small and Cohen (63). —HYDROCHLORIDE, B·HCl+XH_2O, m. p. 190° to 191°, $[\alpha]_D^{23} = +127°$ (water, C=0.693). —METHIODIDE, B·CH_3I, yellow needles, m. p. 187° to 188°. —HYDRIODIDE, B·HI, m. p. 180° to 182° (18) (63).

DIMETHYLAMINOCODIDE: $C_{20}H_{26}O_2N_2$, from α-chlorocodide with dimethylamine, m. p. 118°, forms a hygroscopic HYDROCHLORIDE, and a PLATINICHLORIDE of m. p. 250°. DIETHYLAMINOCODIDE, $C_{22}H_{30}O_2N_2$, melts 102°, PLATINICHLORIDE decomp. 240° (19).

CHLORODIHYDROCODIDE (6) (24): (B=$C_{18}H_{22}O_2NCl$) prep. from dihydrocodeine with PCl_5, cryst. from alcohol, m. p. 172° to 174°. The HYDROCHLORIDE m. at 203°. —METHIODIDE, B·CH_3I, needles from alc. or water, m. p. 244°. It degrades to des-N-methyl-chlorodihydrocodide, $C_{19}H_{24}O_2NCl$ (m. p. 103°) whose Methiodide cryst. in needles of m. p. 272°. On further degradation, trimethylamine is evolved, but the nitrogen-free product is not isolable. Dihydro-des-N-methyl-chlorodihydrocodide, from reduction of the 103° des-base, is an oil whose Methiodide melts 290° to 291° (decomp.). CHLORODIHYDROCODIDE AMINE OXIDE ($C_{18}H_{22}O_3NCl \cdot 3H_2O$), from action of H_2O_2, cryst. from water, m. p. 214° (6). When this is treated with acetic anhydride-sulphuric acid, chlorodihydrocodide-N-oxide sulphonic acid is obtained (decomp. 290° to 295°), which reduces with SO_2 to chlorodihydrocodide sulphonic acid, prisms, decomp. about 300° (52). By the action of HNO_3 in acetic acid a substance $C_{21}H_{24}O_5N_2Cl$ of unknown nature is formed, yellow cryst. from alcohol, m. p. 223° to 224° (6).

The ISOMERS OF CODEINE, preparation and separation: 75 g. of pure α-chlorocodide is treated with 350 c. c. of hot water and brought into solution with the necessary amount of glacial acetic acid, and the solution boiled for three hours, at which time the base precipitated from a sample proves to be halogen-free (4). The reaction mixture is treated with strong KOH until no more precipitate forms, and then extracted with ether; the phenolic by-products remain in the alkaline liquors. The ether is dried over K_2CO_3 and distilled and the half-solid residue dissolved in absol. alcohol, which is then treated with alcoholic HCl to acid reaction. From the well-cooled solution, the pseudocodeine hydrochloride separates after 12 hours. (See also Knorr (10).) The mother liquor is treated with slightly more than the amount of potassium acetate (alcoholic solution) calculated for the HCl present, and after separation of the KCl, alcoholic NaI

is added. After 12 hours, allopseudocodeine hydriodide is completely precipitated. (This hydriodide with ammonia precipitates the base as an oil, which crystallizes from ethyl acetate.) The alcoholic mother liquors are diluted with an equal vol. of water, and the alcohol is removed in vacuo on the water bath. The resulting aqueous solution of isocodeine hydriodide is treated with KOH and ether. The residue from distillation of the ether is taken up in alcohol, and a slight excess of alcoholic oxalic acid added. Isocodeine binoxalate separates after 12 hours. Yield, 27 g. pseudocodeine, 11 g. allopseudocodeine, 16 g. isocodeine (23). For other separations see Knorr (3) (4) (33), Lees (7).

ISOCODEINE: B = $C_{18}H_{21}O_3N$, cryst. from ethyl acetate, m. p. 171° to 172°; $[\alpha]_D = -150.6°$ ($CHCl_3$, C = 1.876) (7). —BINOXALATE, B·$C_2H_2O_4$, cryst. from alcohol, m. p. 235° (3). —METHIODIDE, B·CH_3I, from isocodeine, or from α-isomorphine, leaflets from methyl alcohol, m. p. 270°, $[\alpha]_D^{15} = -102°$ (water, C = 2.40) (3) (27). ISOCODEINE METHYL ETHER METHIODIDE, $C_{19}H_{23}O_3N \cdot CH_3I$, cryst. from alc. or water, m. p. 199° to 200°, $[\alpha]_D^{22} = -111.6°$ (water, C = 0.8555) (17). ISOCODEINE-N-OXIDE, $C_{18}H_{21}O_4N$, prisms from alcohol-ether, decomp. 219° (23). ISOCODEINE-N-OXIDE sulphonic acids, β-form, leaflets from water, blackens 300°; α-form, prisms from water, decomp. 290° (23).

ACETOACETYLISOCODEINE: $C_{22}H_{25}O_5N + \frac{1}{2}C_2H_5OH$, from action of acetic anhydride and H_2SO_4, cryst. dil. alc., m. p. 80° to 85°, solvent-free 105°; $[\alpha]_D^{14} = -236°$ ($CHCl_3$, C = 5.1535) (58).

BROMOISOCODEINE DIBROMIDE: $C_{18}H_{20}O_3NBr_3$, from dil. alcohol, m. p. 212° (23).

DIHYDROISOCODEINE: $C_{18}H_{23}O_3N$, by catalytic reduction, prisms from absol. alcohol, m. p. 199° to 200°; gives a PICRATE, m. p., 235° to 237° and a METHIODIDE, m. p. 272°. The latter yields a des-base of m. p. 151°, whose Methiodide m. 269° and breaks down to a nitrogen-free compound $C_{17}H_{18}O_3$ of m. p. 75° to 76°. ACETYLDIHYDROISOCODEINE cryst. from dil. alcohol, m. p. 166°, forms a Methiodide of m. p. 268° to 269° (23) (39).

ISOCODEINE of Freund (41), from heating dihydrothebaine (phenolic) with dilute acid, $C_{18}H_{21}O_3N$, m. p. 70° to 80°.

PSEUDOCODEINE: B = $C_{18}H_{21}O_3N$, prep. by hydrolysis of chloro- or bromocodides (see above) or methylation of γ-isomorphine (7) (40). Cryst. from ethyl acetate or dil. alcohol (+1 mol. H_2O), m. p. 181° to 182°, $[\alpha]_D = -96.6°$ (alcohol, C = 3.530) (7) (33). It differs from codeine in that it is less soluble in the usual media, and in being precipitated crystalline by ammonia from solutions of its salts (44). —HYDROCHLORIDE, B·HCl, white needles diff. sol. water; sinters at 217° to 218°, decomp. at higher temperatures (44). —HYDROBROMIDE, needles sparingly sol. water, m. p. 228° to 230° (44). —HYDRIODIDE, B·HI + H_2O, cryst. from water, m. p. 260° to 265°, $[\alpha]_D^{15} = -57°$ (water) (26) (33). —SULPHATE, $B_2 \cdot H_2SO_4 + 2H_2O$, leaflets dil. alcohol (2). —NITRATE, long silky needles, sparingly sol. water, redden at 183°, decomp. 190° to 192° (44). —PLATINICHLORIDE, $(B \cdot HCl)_2PtCl_4$, yellow needles from water, decomp. slowly above 214° (44). —MERCURICHLORIDE $(B \cdot HCl)_2 \cdot 3HgCl_2 + 1\frac{1}{2}H_2O$, rods, sparingly sol. in water, sinter 150°, melt 173° to 178° unsharp. (44). —PICRATE, needle clusters, decomp. 209° to 210° (44). —METHIODIDE, B·CH_3I, from methyl alc. or water, m. p. 278° to 279°, $[\alpha]_D^{15} = -50.6°$ (water, C = 1.325); degrades to ε-methylmorphimethine (33) (40).

ACETYLPSEUDOCODEINE, an oil, METHIODIDE also oil, but HYDRIODIDE cryst. from water, m. p. 285° (26). BENZOYLPSEUDOCODEINE, not cryst.; HYDROCHLORIDE melts 174° to 184°, METHIODIDE from methanol, m. p. 206° to 208° (10).

PSEUDOCODEINE PHENYLCARBAMATE, from the action of phenylisocyanate, is an oil; HYDROCHLORIDE cryst. from alcohol, m. p. 73° to 94°; METHIODIDE, from water, m. p. 243° to 244° (10).

ACETOACETYLPSEUDOCODEINE, prisms from alcohol, m. p. 170°, $[\alpha]_D^{18} = -126°$ ($CHCl_3$, C=5.487) (58).

PSEUDOCODEINE-N-OXIDE: $C_{18}H_{21}O_4N + H_2O$, prisms from alcohol, m. p. 226° to 228°. —PICRATE, m. p. 166° to 168°; base yields with acetic anhydride-sulphuric acid isomeric sulphonic acids, decomp. ca. 300° (23) (39).

CHLOROPSEUDOCODEINE: $C_{18}H_{20}O_3NCl$, from action HCl and $KClO_3$, needles from 50% alcohol, m. p. 203° to 204°, $[\alpha]_D^{15} = -100.8°$ (99% alcohol, C=0.4365) (10).

BROMOPSEUDOCODEINE: $C_{18}H_{20}O_3NBr$ ($+C_2H_5OH$), from action bromine-water, needles from alcohol, m. p. 190° to 192°, $[\alpha]_D^{15} = -75.2°$ (99% alcohol, C=0.8385) (10). BROMOPSEUDOCODEINE DIBROMIDE, $C_{18}H_{20}O_3NBr_3$, from bromination of pseudocodeine-N-oxide sulphonate, cryst. from dil. alcohol, m. p. 220°. An oily isomer gives a Hydrobromide in prisms from alcohol, m. p. 235° (23).

NITROPSEUDOCODEINE: $C_{18}H_{20}O_5N_2$, cryst. from absol. alcohol, m. p. 235°, $[\alpha]_D^{15} = -49.9°$ ($CHCl_3$, C=0.6005) (10) (51).

PSEUDOCODEINE METHYL ETHER, from $NaOCH_3$ on α-chlorocodide; m. p. 137°, $[\alpha]_D^{15} = -80°$ (alcohol, C=1.965). —HYDROCHLORIDE, ($+\frac{1}{2}C_2H_5OH$), m. p. 285°, $[\alpha]_D^{20} = -66°$ (water). —HYDRIODIDE, m. p. 238° to 240°. —SULPHATE, m. p. 241°. —NITRATE, m. p. 219°. —METHIODIDE, decomp. 270° to 271° (14) (15) (16) (17), which degrades to ϵ-methylmorphimethine methyl ether.

PSEUDOCODEINE ETHERS (15) (16): ETHYL, m. p. 76°; -Hydrochloride, 255°; -Hydriodide, m. p. 267° to 270°. PROPYL, not cryst; -Hydriodide, m. p. 259°. PHENYL, m. p. 187°. p-CRESYL, m. p. 165°, $[\alpha]_D^{20} = -13.7°$ ($CHCl_3$); -Hydrochloride, 231°; -Nitrate, 181°. m-CRESYL, m. p. 144°; -Nitrate, 192°. o-CRESYL, m. p. 189°. GUAIACYL, m. p. 214°, $[\alpha]_D^{20} = -22.9°$ ($CHCl_3$); -Nitrate, 197°; -Oxalate, 197°; -Tartrate, 205°.

CYANONORPSEUDOCODEINE METHYL ETHER, from action of CNBr, needles from alcohol, m. p. 170° to 172° (50). CYANONORPSEUDOCODEINE PHENYL ETHER, m. p. 171° (50).

DIHYDROPSEUDOCODEINE: $C_{18}H_{23}O_3N$, by electrolytic or sodium-alcohol reduction of pseudocodeine; needles from alcohol, m. p. 128°; soluble in alkali. It gives a METHIODIDE, leaflets from water, decomp. 275°; degradation products not cryst. (23).

TETRAHYDROPSEUDOCODEINE (23) (39): $C_{18}H_{25}O_3N + \frac{1}{2}H_2O$, from catalytic reduction of pseudocodeine; prisms from alcohol, m. p. 114° to 115°, $[\alpha]_D^{21} = -17.8°$ (alcohol, C=1.0592), alkali-soluble. —HYDROCHLORIDE (from alcohol), decomp. 238° to 240°. —METHIODIDE, decomp. 249° to 250°; it gives a des-base of m. p. 162° to 163°, $C_{19}H_{27}O_3N$. DIACETYLTETRAHYDROPSEUDOCODEINE is obtained as leaflets from dil. alcohol, m. p. 137° to 138°. TETRAHYDROPSEUDOCODEINE METHYL ETHER is obtained as the Methiodide, leaflets from water, m. p. 247°.

ALLOPSEUDOCODEINE (β-Isocodeine): B=$C_{18}H_{21}O_3N$. Prep. from chloro- or bromo- codides as outlined above. (See also Knorr (33).) From methylation of β-isomorphine. (See Lees. (7) (54).) Needles from ethyl acetate, m. p. 116° to 117°, $[\alpha]_D^{21} = -235.4°$ (alcohol, C = 1.6992) (23). —HYDRIODIDE, B·HI, cryst. from water, decomp. 280° to 285°, $[\alpha]_D^{15} = -153°$ (water, C =1.967) (33). —METHIODIDE, B·CH_3I, cryst. from alcohol, m. p. 215° to 216°, $[\alpha]_D^{15} = -142°$ (water, C = 1.728) (3) (7) (33) (54).

ACETYLALLOPSEUDOCODEINE, needles from alcohol, m. p. 194° to 195°; -Methiodide, m. p. 260° (33).

ACETOACETYLALLOPSEUDOCODEINE, from acetic anhydride and H_2SO_4, oil (58).

BROMOALLOPSEUDOCODEINE DIBROMIDE: $C_{18}H_{20}O_3NBr_3$, from bromine-water on the N-oxide sulphonate; cryst. from alcohol, m. p. 206° to 207° (23).

ALLOPSEUDOCODEINE-N-OXIDE SULPHONATE, occurs in isomeric forms, m. p. 271° and decomp. 280°, respectively (23).

MOLECULAR COMPOUND, with isocodeine, m. p. 147° to 147.5° (7) (23).

TETRAHYDROALLOPSEUDOCODEINE (23): $C_{18}H_{25}O_3N$, by catalytic reduction in dil. acetic acid with colloidal Pd; leaflets from dil. alcohol, m. p. 137° to 138°, $[\alpha]_D^{21} = -75°$ (alcohol, C=1.4136); soluble in alkali. Diacetyl deriv. m. at 115°. The Methiodide, needles from water m. 252°, yields an oily des-base whose Hydriodide m. 236°.

α-CHLOROMORPHIDE: B=$C_{17}H_{18}O_2NCl$, prep. from morphine with PCl_3 (40) (55), with dry liquid HCl (56), or thionyl chloride (8). Twenty g. of morphine (dried at 100° in vacuum) is added slowly with strong cooling to 40 g. thionyl chloride. After all is in solution, it is allowed to stand an hour at room temperature, and the excess of $SOCl_2$ removed in vacuum without heating. The viscous mass is brought into solution in ice water and the base precipitated by exactly the necessary amount of soda. Recryst. from methyl alcohol; 70% to 90% yield, m. p. 193° (8); m. p. 204° (decomp.) when rapidly heated (40). $[\alpha]_D = -375.2°$ (CH_3OH, C=0.573); sol. in $CHCl_3$, methyl or amyl alcohol, sparingly in alcohol or ether, insol. in most other organic solvents (55). —HYDROCHLORIDE, B·HCl, recryst. from alcohol; $[\alpha]_D^{20} = -315.3°$ (water, C=1.67) (55). —HYDROBROMIDE, B·HBr, recryst. alcohol; $[\alpha]_D^{19} = -268.6°$ (C=1.65) (55). —METHIODIDE, B·CH_3I, prisms from methyl alcohol, m. p. 207° (corr.) (56).

ACETYLCHLOROMORPHIDE: $C_{19}H_{20}O_3NCl$, cryst. from absol. alcohol or acetone, m. p. 174° to 178°. —HYDROCHLORIDE, silky needles (55). CHLOROCYANONORMORPHIDE, $C_{17}H_{15}O_2N_2Cl$, from $SOCl_2$ on cyanonormorphine, decomp. 300°; Diethylaminocyanonormorphide, m. p. 248° (60).

β-CHLOROMORPHIDE: B=$C_{17}H_{18}O_2NCl$, prep. from morphine and fuming HCl at 65°, or from α-chloromorphide; prisms from ether, m. p. 188° (57), $[\alpha]_D^{15} = -5°$ (CH_3OH, C=3.975) (3). Sol. alcohol, benzol, sparingly in ether. —NITRATE, crystalline. —METHIODIDE, B·CH_3I, cryst. from water, m. p. 210° (decomp.) (57).

ACETYL-β-CHLOROMORPHIDE, needles from alcohol, m. p. 163°, giving a cryst. HYDROCHLORIDE, and a METHIODIDE of m. p. 177° (57).

SULPHO-β-CHLOROMORPHIDE: $C_{17}H_{18}O_5NClS + H_2O$, from action of conc. H_2SO_4; crystallizes from water; with boiling water it yields a chlorine-free sulpho product (57).

CHLORODIHYDROMORPHIDE (24): $C_{17}H_{20}O_2NCl$, from chlorodihydrocodide with HI and red phosphorous; prisms, m. p. 155°, solidifying and m. again at 233° to 235°. Best prepared by refluxing dihydromorphine with thionyl chloride (62).

BROMOMORPHIDE: B=$C_{17}H_{18}O_2NBr$. Prep. from morphine or α-isomorphine with PBr_3 or 45% HBr (27)(55)(59), or liquid HBr (56); recryst. by extraction with dry ether; m. p. 169° to 170°, $[\alpha]_D^{25} = +65.9°$ (CH_3OH, C=2.837). Soluble in chloroform, alcohol, benzene, ethyl acetate, sparingly in ether. —HYDROCHLORIDE, B·HCl + H_2O (from water or alcohol); $[\alpha]_D^{27} = +41.1°$ (C=3.157). —HYDROBROMIDE, B·HBr + H_2O (from alcohol), m. p. 196°, $[\alpha]_D^{25} = +39.5°$ (C=2.53). —METHIODIDE, B·CH_3I, needles m. p. 200° (56).

BROMOMORPHIDE PHENYLCARBAMATE: $C_{24}H_{23}O_3N_2Br$, by action of phenylisocyanate, needles, m. p. 204° (56).

DIETHYLAMINOMORPHIDE: $C_{21}H_{28}O_2N_2$, from chloromorphide with diethylamine; cryst. from abs. alcohol, m. p. 203°, soluble in alkali, $FeCl_3$ reaction. The Monomethiodide decomp. 268° (8).

α-ISOMORPHINE: B=$C_{17}H_{19}O_3N$, prep. by boiling α-chloro- or bromomorphide with water or dilute acetic acid (40) (55); the mixture of isomeric morphine hydrohalides thus obtained is treated with soda and the morphines separated by differences in solubility in acetone. Cryst. in needles from methyl alcohol-

ethyl acetate; m. p. 251° to 252°, $[\alpha]_D^{15} = -167°$ (CH_3OH, C=2.952). Soluble in methyl alcohol, sparingly in ethyl alcohol, and hot water. —HYDROCHLORIDE, B·HCl (from alcohol); $[\alpha]_D^{20} = -150°$ (C=4.76). —HYDROBROMIDE, B·HBr+H_2O (from water); $[\alpha]_D^{15} = -127.2°$ (C=2.49). —METHIODIDE, B·CH_3I, by refluxing in methyl alcohol with CH_3I; cryst. from water, m. p. 276°, $[\alpha]_D^{23} = -91.5°$ (water, C=1.696) (55). By the action of silver sulphate and barium hydroxide on this, a quaternary base of phenol-betaine structure is obtained; it reacts directly with methyl iodide to give isocodeine methiodide. For degradation see γ-methylmorphimethine.

DIACETYL-α-ISOMORPHINE, not cryst., yields a Methiodide, silky needles from methyl alcohol, m. p. 241° to 242° (27).

β-ISOMORPHINE: B=$C_{17}H_{19}O_3N$, prep. by hydrolysis of α-chloromorphide or bromomorphide (27) (40); cryst. from alcohol (with $\frac{1}{2}C_2H_5OH$) m. p. 182°, $[\alpha]_D^{17} = -216.2°$ (CH_3OH, C=1.634); sol. acetone, benzene, chloroform, water, sparingly in alcohol, insol. ether or ligroin. —HYDROCHLORIDE, B·HCl, prismatic needles from water, $[\alpha]_D^{11} = -200.8°$ (water, C=2.257) (27). —METHIODIDE, B·CH_3I, cryst. from water, m. p. 250°, $[\alpha]_D^{23} = -146.1°$ (water, C=2.178) (27).

γ-ISOMORPHINE (Neoisomorphine): B=$C_{17}H_{19}O_3N$, prep. by hydrolysis of the halogenomorphides (7) (33) (40) (54). Cryst. from alcohol with $1C_2H_5OH$, m. p. 278°, $[\alpha]_D^{15} = -94°$ (CH_3OH, C=1.795), diff. sol. in most organic solvents. —HYDROCHLORIDE, m. p. 314°, $[\alpha]_D^{15} = -76°$ (water, C=1.888). —HYDROBROMIDE, m. p. 298°, $[\alpha]_D^{15} = -71°$ (water, C=1.885). —METHIODIDE, m. p. 293°, $[\alpha]_D^{15} = -50°$ (water, C=1.5404).

DIACETYL-γ-ISOMORPHINE, not cryst., gives a Methiodide in needles from alcohol, m. p. 267°, $[\alpha]_D^{15} = -24°$ (water, C=1.273) (40).

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THE THIOCODIDES

The alkyl thiocodides of general formula $C_{18}H_{20}O_2NSR$, which may be regarded as the sulphalkyl analogs of the halogenocodides, result from the action of mercaptans on α- or β-chlorocodide or bromocodide. Alkyl thiomorphides are also known, but have been only very slightly studied.

The corresponding sulphohydryl derivatives do not appear to be capable of independent existence. While potassium hydrosulphide reacts with the halogenomorphides to replace halogen with the sulphohydryl group, a simultaneous oxidation takes place, through which two molecules are united to give the dimolecular product, bis-thiomorphide

$$2C_{17}H_{18}O_2NCl + 2KSH \longrightarrow (2C_{17}H_{18}O_2NSH) + O \longrightarrow (C_{17}H_{18}O_2NS)_2$$

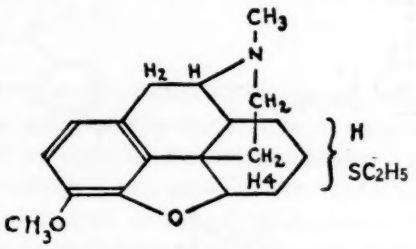
Bis-thiomorphide methylates to bis-thiocodide, which may also be obtained by the action of potassium hydrosulphide on bromocodide (1).

The ethylthiocodides, which have been most studied, are known in four forms (2). α-Ethylthiocodide is the chief product obtained when β-chlorocodide or bromocodide is treated with ethylmercaptan in aqueous alkali at 100°.

β-Ethylthiocodide is formed by a rearrangement of the α-form when it is heated with sodium alcoholate, and therefore results directly when bromocodide reacts with mercaptan in alcoholic solution in the presence of excess sodium ethylate. As a by-product of the last-mentioned reaction, a third isomer, γ-ethylthiocodide, may be isolated in very small amount.

δ-Ethylthiocodide, the fourth isomer, is prepared by heating α-chlorocodide with mercaptan and sodium alcoholate.

The nature of the isomerism of the ethylthiocodides is not known. They may be represented by the following type formula:



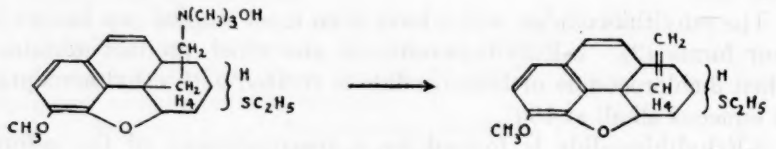
Pschorr regarded them as analogous to the four isomeric codeines, which concept is, however, open to objections because of the peculiarities exhibited by β-ethylthiocodide. This isomer is exceptional in many respects, and will be considered below after the general behavior of the other three isomers has been discussed.

α-, γ-, and δ-Ethylthiocodides form normal methiodides, which degrade by the Hofmann method to isomeric ethylthiomethylmorphimethines. α-Ethylthiomethylmorphimethine, from α-ethylthiocodide methiodide, isomerizes with sodium alcoholate to a β-form. γ- and δ-Ethylthiomethylmorphimethine, from γ- and δ-ethylthiocodide methiodide, respectively, do not undergo such a rearrangement.

The similarity in behavior of these methine bases to that of the methylmorphimethines (p. 268) led Pschorr to suspect that γ- and δ-ethylthiocodide must be of the pseudocodeine- allopseudocodeine type, while α-ethylthiocodide would be comparable to codeine or isocodeine. The β-ethylthiomethylmorphimethine mentioned above can also be prepared by treating α-chloromethylmorphimethine (p. 273) with mercaptan in the presence of sodium alcoholate, or from the peculiar reaction product from β-ethylthiocodide and methyl iodide which is described in a later paragraph.

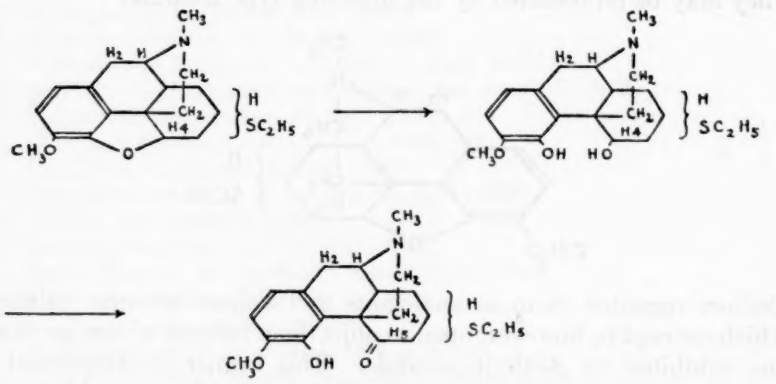
The ethylthiomethylmorphimethines, with the exception of the δ-isomer, yielded noncrystalline products on degradation. In marked contrast to most

nitrogen-free end products from unhydrogenated morphine series, a substance which contains a vinyl group results from decomposition of δ-ethylthiomethylmorphimethine methohydroxide.



β-Ethylthiocodide

The reactions of β-ethylthiocodide, especially with hydrochloric acid and with methyl iodide, are unique. When warmed with hydrochloric acid it adds a molecule of water, and yields a phenolic ketone, $C_{17}H_{18}N(OCH_3)(OH)(=O)(SC_2H_5)$, which will hereafter be referred to as the thioketone. The natural conclusion that the thioketone is formed through hydrolytic scission of the ether bridge, whereby a phenolic hydroxyl and the enol form of a keto group are formed,



is made improbable through evidence to be presented in a later paragraph, which shows that the sulphethyl group has shifted in the reaction. Pschorr therefore suggested that the keto group was formed at some time during the probable hydrolytic removal of the sulphethyl group and its recombination at another point.

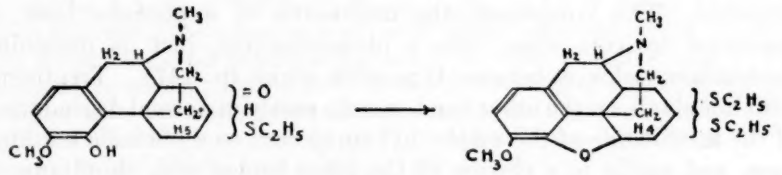
When hydrochloric acid acts on β-ethylthiocodide in the cold, two new compounds may be isolated. One of these is a sulphur-free phenolic ketone, $C_{18}H_{21}O_3N$, an isomer of thebainone (p. 308). The other, diethyldithiocodide, $C_{18}H_{21}O_2N(SC_2H_5)_2$, is an addition product of β-ethylthiocodide with the mercaptan liberated in the formation of the sulphur-free ketone. These two products represent an intermediate stage in the reaction which results in the thioketone described above, for if they are warmed together in hydrochloric acid the dimercaptyl compound takes up a molecule of water and loses mercaptan to the sulphur-free ketone, and the sole product is the thioketone.

The thioketone and sulphur-free ketone are mutually interconvertible. The sulphur-free ketone is extracted by chloroform from an alkaline solution of the thioketone; on the other hand, when a dilute alkaline solution containing the sulphur-free ketone and mercaptan is treated with ammonium carbonate, the thioketone is precipitated. When a solution of the thioketone in dilute hydrochloric acid is boiled, mercaptan is evolved and the sulphur-free ketone results.

The thioketone undergoes a remarkable change in the presence of mercaptan and hydrochloric acid; a molecule of mercaptan is added, loss of water takes place, and the resulting product is diethyldithiocodide,

$$C_{18}H_{22}O_3NSC_2H_5 + HSC_2H_5 \longrightarrow C_{18}H_{21}O_2N(SC_2H_5)_2 + H_2O$$

This was the first example of re-formation of the 4, 5-ether bridge in morphine chemistry.[82]



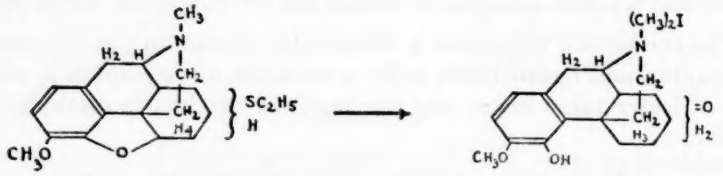
As has been mentioned, evidence has been found which indicates that the sulphalkyl group in the thioketone is at a different position from that which it occupies in β-ethylthiocodide. It was observed that isomeric disulphalkyl compounds were obtained when, on the one hand methylmercaptan and β-ethylthiocodide (Equation 1), on the other hand ethylmercaptan and β-methylthiocodide (Equation 2), were allowed to react in the presence of a little hydrochloric acid:

$$C_{18}H_{20}O_2N(SC_2H_5) + HSCH_3 = C_{18}H_{21}O_2N(SC_2H_5)(SCH_3) \quad (1)$$
$$C_{18}H_{20}O_2N(SCH_3) + HSC_2H_5 = C_{18}H_{21}O_2N(SCH_3)(SC_2H_5) \quad (2)$$

β-Methylthiocodide, like its homologue, when warmed with hydrochloric acid undergoes a reaction which yields a phenolic thioketone, $C_{18}H_{22}O_3N(SCH_3)$, which in this case, contains a sulphomethyl group. This substance adds ethylmercaptan, with loss of a molecule of water to give the dialkyldithiocodide of Equation 1, whereas that of Equation 2 would be expected if the sulphomethyl group in the ketone occupied the same position as it did in β-methylthiocodide. While this is not direct proof of a shift of the sulphethyl group in the analogous transformations of β-ethylthiocodide, it constitutes good evidence that the reaction involves some very complicated changes, and no direct conclusions concerning the structure of the substances involved are justified.

[82] The only other case known outside of those described in the ethylthiocodide series is that recently found by Schöpf, Ann. 483, 157, 169 (1930); see Thebainone, p. 312.

Methyl iodide acts on β-ethylthiocodide in the presence of water in a most remarkable way, to give the methiodide of a phenolic ketone which is identical with the methiodide of the above-mentioned sulphur-free phenolic ketone.



If the reaction is carried out in cold anhydrous chloroform, the ether bridge is opened to form a phenolic hydroxyl, as in the above case; but no keto group appears, and the sulphethyl radical remains in the molecule. This compound, the methiodide of a phenolic base, is converted by cold alkali into a phenol-betaine, just as morphine methiodide yields a betaine type with alkali (p. 147). Treatment with hot alkali, on the other hand, results partly in normal degradation of the methiodide of the sulphethyl compound to a phenolic methine base, and partly in a closure of the ether bridge with simultaneous degradation to β-ethylthiomethylmorphimethine.

The extraordinary reactions of methyl iodide with β-ethylthiocodide are unparalleled; in no other case in morphine chemistry has a breakage of the 4, 5-ether bridge by this reagent been observed.

β-Ethylthiocodide is transformed by acetic anhydride at 100° into the acetyl derivative of a phenolic base through opening of the ether bridge. When the acetyl compound is warmed with alkali, saponification takes place, and the ether ring closes again to give the starting material, β-ethylthiocodide. The opening of the 4, 5-ether ring in anhydrous medium was assumed by Pschorr (3) to take place at the expense of hydrogen from ring III of the nucleus, which thereby went over into a dihydrogenated ring with formation of a new double linkage. This process, for the sake of illustration, may be depicted as below, in which it will be understood that no evidence exists for the location either of the substituents or the unsaturated linkages.

In analogy with bromocodide, bromomorphide may be converted to ethylthiomorphides (4), one of which, β-ethylthiomorphide, behaves like β-ethylthiocodide toward hydrochloric acid or acetic anhydride.

The peculiar reactions described in this section do not appear to be limited to β-ethylthiocodide, for preliminary experiments (3) showed that pseudocodeinone (p. 251) reacts with mercaptan in the presence of hydrochloric acid to give an amorphous nonphenolic compound, whose methiodide ($C_{21}H_{28}O_3NIS + CH_3OH$, m. p. 204° corr.) is apparently a phenol.

Descriptive Part (The Thiocodides)

BIS-THIOMORPHIDE (1): $(C_{17}H_{18}O_2NS)_2$, prep. by refluxing chloro- or bromomorphide with alcoholic potassium hydrosulphide. Cryst. from chloroform in needles, m. p. 201°.

BIS-THIOCODIDE (1): $(C_{18}H_{20}O_2NS)_2$, prep. from bromocodide with alcoholic potassium hydrosulphide; cryst. from alcohol in leaflets of m. p. 200° (corr.). It is soluble in alkali. —METHIODIDE, needles, m. p. 253°.

α-ETHYLTHIOCODIDE (2): $C_{20}H_{25}O_2NS$, prep. from bromocodide or β-chlorocodide by shaking 4 hours at 100° with ethylmercaptan in 2.5 *N* sodium hydroxide. Cryst. from ligroin in prisms of m. p. 88° to 89°, $[\alpha]_D^{26} = -340°$ (alcohol, C=0.8940). The HYDRIODIDE cryst. in leaflets from alcohol or water, m. p. 217° (corr.). The METHIODIDE decomp. 236° to 237° (corr.), $[\alpha]_D^{20} = -232.6°$ (water, C=0.720); it degrades to α-ETHYLTHIOMETHYLMORPHIMETHINE, noncrystalline, whose Hydriodide, $C_{21}H_{28}O_2NIS$, decomp. 204° to 206° (corr.) and Methiodide cryst. in needles decomp. at 235° to 236° (corr.), $[\alpha]_D^{26} = -183°$ (water, C=0.2185).

β-ETHYLTHIOCODIDE (1) (2): $C_{20}H_{25}O_2NS$, prep. by boiling α-ethylthiocodide in alcohol with sodium ethylate, or by boiling bromocodide with ethylmercaptan and alcoholic sodium ethylate. Cryst. from alcohol, m. p. 148°. The HYDROCHLORIDE decomp. easily, giving off ethylmercaptan. With cold dilute HCl are formed: DIETHYLDITHIOCODIDE (3), noncrystalline, insol. in alkali, whose Methiodide cryst. from water in needles, decomp. 212° to 213° (corr.), and the SULPHUR-FREE KETONE, $C_{18}H_{21}O_3N + \frac{1}{2}H_2O$, cryst. from ethyl acetate m. p. 145° to 147°, $[\alpha]_D^{26} = -42.5°$ (alcohol, C=1.931), whose Hydriodide ($+H_2O$) m. at 165°, solidifies and decomp. 265°. The Methiodide cryst. from water in leaflets decomp. 251°. The Acetyl derivative of the sulphur-free ketone was isolated as the hydriodide, needles, decomp. 269°. The Oxime hydrochloride of the sulphur-free ketone cryst. in needles from water, decomp. 282° to 283°; the free Oxime, leaflets from ethyl acetate, decomp. 175° to 177°. The Semicarbazone decomp. 247° to 248°. The sulphur-free ketone is best prepared by boiling β-ethylthiocodide with dilute hydrochloric acid.

The THIOKETONE (3): $C_{20}H_{27}O_3NS + H_2O$, from warming β-ethylthiocodide on the water bath for 30 minutes with 2 *N* hydrochloric acid. Leaflets from acetone, m. p. 121° to 127°, anhydrous it melts at 182°; soluble in alkali. —HYDRIODIDE, felted needles decomp. 222° to 223° (corr.). —METHIODIDE, decomp. 241° (corr.). —OXIME, m. p. 258° (corr.).

ETHYLMETHYLDITHIOCODIDE (3): $C_{21}H_{29}O_2NS_2 + CH_3OH$, from addition of methylmercaptan to β-ethylthiocodide; plates from methanol, m. p. 71° to 73°. —METHIODIDE, decomp. 146° to 147°, $[\alpha]_D^{20} = +24°$ (water, C=0.193).

β-METHYLTHIOCODIDE (3): $C_{19}H_{23}O_2NS$, prep. by refluxing bromocodide with methylmercaptan and alcoholic sodium ethylate. It cryst. from alcohol in prisms of m. p. 124° to 125°. β-Methylthiocodide, warmed with dil. HCl, yields a phenolic ketone $C_{19}H_{25}O_3NS$ containing the sulphomethyl group, prisms from alcohol, m. p. 141° to 142°.

METHYLETHYLDITHIOCODIDE (3): $C_{21}H_{29}O_2NS_2$, prisms of m. p. 112° to 115°, giving a METHIODIDE decomp. 184°, $[\alpha]_D^{20} = +33.6°$ (water, C=0.201).

β-ETHYLTHIOCODIDE WITH METHYL IODIDE (3): In aqueous alcoholic solution, yields the methiodide (m. p. 251°) of the sulphur-free ketone. In anhydrous $CHCl_3$, it yields the METHIODIDE of a phenolic sulphur-containing compound, $C_{21}H_{28}O_2NSI$, flat needles, decomp. 232°, whose Acetyl derivative m. 161°. The methiodide with alkali gives a BETAINE, $C_{21}H_{27}O_2NS$ of m. p. 170° to 172°. The betaine with methyl iodide gives a Methyl ether methiodide of m. p. 209° to 211°.

β-ETHYLTHIOMETHYLMORPHIMETHINE (2) (3): $C_{21}H_{27}O_2NS$, prep. by rearrangement of the α-methine, from bromocodide methiodide with mercaptan in boiling sodium alcoholate solution, or from chloromethylmorphimethine with mercaptan and sodium ethylate. It cryst. in yellow leaflets from alcohol, m. p. 173° to 174° (corr.). —METHIODIDE, needles, decomp. 124° to 125°.

γ-ETHYLTHIOCODIDE (2) was obtained amorphous from the mother liquors of β-ethylthiocodide preparation. —METHIODIDE, $C_{21}H_{28}O_2NIS$, decomp. 265° to 266°, $[\alpha]_D^{20} = -119.2°$ (water, C=0.2475). It degrades to γ-ETHYLTHIOMETHYLMORPHIMETHINE, oily, whose Hydriodide, $C_{21}H_{28}O_2NIS$, m. 179° to 180° (corr.), $[\alpha]_D^{20} = -161°$ (water, C=0.1955).

δ-ETHYLTHIOCODIDE (2), prep. by refluxing α-chlorocodide with ethylmercaptan and sodium ethylate in alcohol solution; the base is poorly crystallized. —HYDRIODIDE, $C_{20}H_{26}O_2NIS$, decomp. 255° (corr.), $[\alpha]_D^{20} = +51.4°$ (water, C=0.2235). —METHIODIDE, prisms decomp. 230° to 234° (cryst. from alcohol, m. p. 143° to 145°); $[\alpha]_D^{20} = +55°$ (water, C=0.6185). It degrades to δ-ETHYLTHIOMETHYLMORPHIMETHINE, an oil whose Hydriodide m. 196° to 197° (corr.), $[\alpha]_D^{20} = +49°$ (water, C=0.2035), and whose Methiodide m. 193° to 195° (corr.), $[\alpha]_D^{20} = +39°$ (water, C=0.1925). The last-named degrades to trimethylamine and a TETRAHYDROVINYLSULPHETHYLMORPHENOL METHYL ETHER, $C_{19}H_{20}O_2S$, prisms of m. p. 97° to 100°, $[\alpha]_D^{20} = +689°$ (alcohol, C=0.0546).

β-ETHYLTHIOMORPHIDE (4): $C_{19}H_{23}O_2NS$, prep. by refluxing bromomorphide hydrobromide with mercaptan and sodium ethylate in alcohol; cryst. from methyl alcohol, decomp. 200° to 202°.

DIETHYLDITHIOMORPHIDE (4): $C_{21}H_{29}O_2NS_2$, prep. by treatment of β-ethylthiomorphide with cold dil. HCl; prisms decomp. 252°. In the same reaction is formed the corresponding: SULPHUR-FREE KETONE (4), $C_{17}H_{19}O_3N$, leaflets decomp. 215° to 217°, whose Oxime decomp. 260°, and Diacetyl derivative methiodide decomp. 255° to 258°.

SULPHUR-CONTAINING KETONE: $C_{19}H_{25}O_3NS$, from β-ethylthiomorphide with warm dil. HCl, needles decomp. 205° to 208°. Its OXIME HYDROCHLORIDE ($+H_2O$) is crystalline.

β-ETHYLTHIOMORPHIDE WITH ACETIC ANHYDRIDE (4), yields an amorphous Diacetyl derivative whose methiodide $C_{24}H_{30}O_4NIS + C_2H_6O$ decomp. 153°.

ISOMERIC ETHYLTHIOMORPHIDE (4): $C_{19}H_{23}O_2NS$, leaflets decomp. 180°.

Bibliography (The Thiocodides)

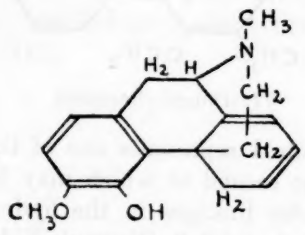
(1) Pschorr, Ber. **39**, 3130 (1906).
(2) Pschorr and Rollett, Ann. **373**, 1 (1910).
(3) Pschorr, Ann. **373**, 15 (1910).
(4) Pschorr and Hoppe, Ann. **373**, 45 (1910).

THE DESOXYCODEINES

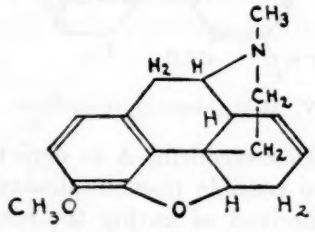
The name desoxycodeine has been used to designate the phenolic base $C_{18}H_{21}O_2N$ containing one less oxygen atom than codeine, which was first described and investigated by Knorr and Waentig (1).[83] The

[83] A desoxycodeine of the same formula was mentioned by Wright (2) as resulting from the action of hot hydrobromic acid on codeine. It has never been further investigated, and nothing is known of its structure.

term "desoxycodeine" for the phenolic base (I) was unfortunately chosen, since it should logically refer to the hypothetical base of Formula II which still contains the codeine skeleton intact.



I. Desoxycodeine-A



II. Hypothetical Desoxycodeine

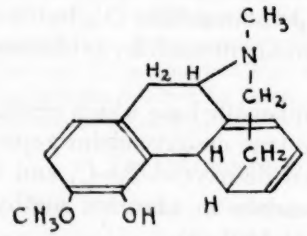
With the discovery of a base of this type, as well as of a second phenolic desoxy-base, it became necessary to change the name of the Knorr compound to desoxycodeine-A (3).

Desoxycodeine-A is prepared by refluxing α-chlorocodide, or bromocodide, with zinc dust in absolute alcohol (1), and must result from addition of one molecule of hydrogen to the halogenocodide, followed by loss of hydrogen halide, or the equivalent of this process (4).

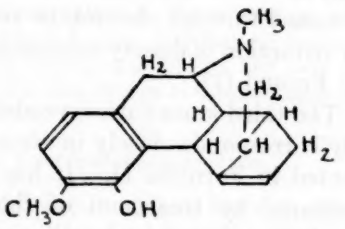
Desoxycodeine-A is the chief product formed when methyl or ethyl magnesium iodide acts on α-chlorocodide; iodocodide (p. 215) apparently forms an intermediate step in the reaction (3).

Desoxycodeine-A is also produced when pseudochlorocodide (1) (5), β-chlorocodide (6), or iodocodide (3) is reduced with zinc and alcohol. This has been taken as evidence that the fundamental structural skeleton of the isomeric codeines and halogenocodides is the same.

In addition to the Robinson formula (I) given above, desoxycodeine-A has been represented as in III and IV.

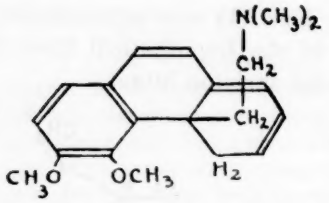


III. Desoxycodeine (Knorr-Freund (1) (7))

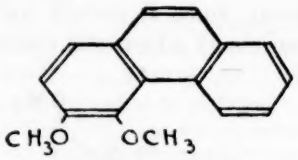


IV. Desoxycodeine (Freund (7))

The Hofmann degradation of the amorphous desoxycodeine-A methiodide leads to a crystalline but very sensitive des-N-methyldesoxycodeine-A (desoxycodomethine) which oxidizes rapidly in air. Proceeding from desoxycodeine-A methyl ether methiodide the unstable methyldesoxycodomethine is obtained, which decomposes spontaneously to an amine and dimethylmorphol (1).

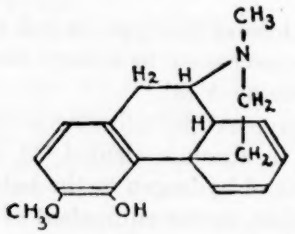


V. Methyldesoxycodomethine



VI. Dimethylmorphol

Desoxycodeine-A as depicted in Formula I represents one of the two possible phenolic desoxycodeines, the second of which may be conceived as having the conjugated double linkages in the hydroaromatic ring in the alternative positions 5, 6- and 7, 8- (Formula VII).



VII. Desoxycodeine-B

This compound, desoxycodeine-B, of m. p. 119° is formed when α-chlorocodide in dilute sulphuric acid is reduced by the electrolytic method (3). This reaction, which was first carried out by Freund (7), was believed to result in a dihydrodesoxycodeine; the supposed dihydrodesoxycodeine can, however, like desoxycodeine-A, be reduced with addition of two or four atoms of hydrogen (see below) to a dihydro- or tetrahydro-desoxycodeine. Desoxycodeine-B is likewise obtained through electrolytic reduction of β-chlorocodide (3), but not by reduction of desoxycodeine-A or of chlorodihydrocodide, as claimed by Freund (7).

The third known desoxycodeine is a nonphenolic base which probably corresponds closely in structure to the true desoxycodeine represented in Formula II. It has been named desoxycodeine-C, and is prepared by treatment of chlorodihydrocodide in absolute methyl alcoholic solution with sodium methylate at 140° (3).

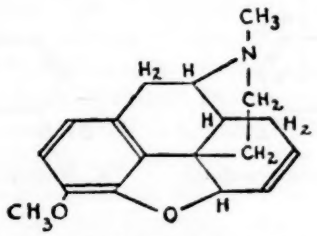
Knoll & Co. (8), using this method, claimed to have obtained from the reaction a dihydrodesoxycodeine; such a conversion of $C_{18}H_{22}O_2NCl$ to $C_{18}H_{23}O_2N$ would involve a most unusual reduction, whereas the formation of a desoxycodeine necessitates only splitting out a molecule of hydrochloric acid (3).

On heating chlorodihydrocodide with sodium methylate at 120°, Mannich and Löwenheim (9) observed no reaction.

Desoxycodeine-C reduces electrolytically to a phenolic base, dihydrodesoxycodeine-B (see below) which may be further reduced catalytically to tetrahydrodesoxycodeine. When desoxycodeine-C is

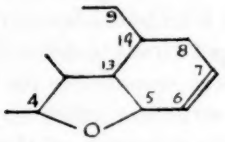
reduced by the catalytic method it absorbs two molecules of hydrogen to give tetrahydrodesoxycodeine directly (3).

From the fact that desoxycodeine can not be reduced without a rupture of the ether bridge, Small and Cohen (3) reason that the double linkage in ring III probably occupies the 6, 7-position (Formula VIII).



VIII. Desoxycodeine-C

As evidence for this is advanced the behavior of other compounds which are believed to have an unsaturation in this position. Whereas codeine and isocodeine, and the α-, β-, γ-, and δ-methylmorphimethines (see p. 268) can be reduced by simple saturation of the double linkage at 7, 8 or 8, 14 to yield nonphenolic dihydro products, pseudocodeine and allopseudocodeine, as well as ϵ-and ζ-methylmorphimethines take up two more hydrogen atoms than the isomeric substances mentioned, to give phenolic tetrahydro derivatives. As Schöpf (10) has pointed out, the behavior of the grouping –O–CH–CH=CH–



generally accepted as being present in the last-named group of compounds is to a certain degree comparable with that of a conjugated system of double linkages, –CH=CH–CH=CH–, and the fact that hydrogenation of the substances mentioned takes place always with opening of the 4, 5-ether ring may be explained through the assumption that a 1, 4-addition of hydrogen (at –O– and C-7) first takes place, followed by saturation of the 5, 6-double linkage in the intermediately formed compound.

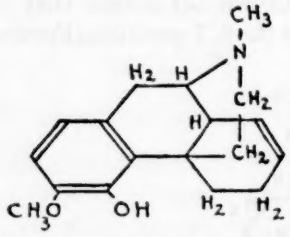
The Dihydrodesoxycodeines and Tetrahydrodesoxycodeine

The reduction products of desoxycodeine-A and its isomers are of considerable importance for the theory of morphine structure, and have had a marked influence on speculations concerning the structural relationships among certain isomeric compounds in the morphine series.[84]

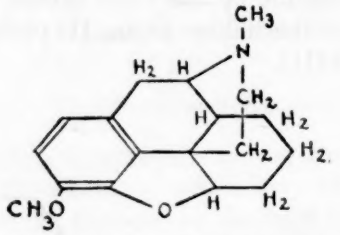
If the possibility of isomerism due to differences in the spatial arrangement of the hydrogen atom on C-14 be disregarded, there are theoretically possible four phenolic dihydrodesoxycodeines of type

[84] See, for example, Gulland and Robinson, J. Chem. Soc. **123**, 984, 1000 (1923); Schöpf, Ann, **452**, 239, 240 (1927); Ann. **458**, 155, 159, 164 (1927); Wieland and Kotake, Ann. **444**, 80 (1925).

IX, in which the isomerism is due to differences in position of the hydroaromatic double bond, and one nonphenolic dihydrodesoxycodeine (X).



IX. Phenolic Dihydrodesoxycodeine



X. Nonphenolic Dihydrodesoxycodeine

All of these are known, and largely through the investigations of Small and Cohen (11) their relationship to tetrahydrodesoxycodeine and to some of the desoxycodeines has been established.

Dihydrodesoxycodeine-A (m. p. 134° to 135°) is obtained by reduction of desoxycodeine-A or of α-chlorocodide, with sodium and alcohol (11). This preparation was first carried out by Knorr (1), who named the product desoxydihydrocodeine.[85] In a later investigation, Freund (7) believed to have shown that Knorr's desoxydihydrocodeine was actually a tetrahydrodesoxycodeine (designated as "α"-), isomeric with the tetrahydrodesoxycodeine (β-) which results from addition of 4 hydrogen atoms to desoxycodeine-A by the catalytic method. This concept was responsible for considerable confusion in the theory of morphine structure, since any acceptable formula was obliged to account for the existence of these two supposed isomers. The isomerism was eliminated in 1931, when it was found (11) that the supposed α-tetrahydrodesoxycodeine reduced catalytically with absorption of one molecule of hydrogen to give (β-) tetrahydrodesoxycodeine. It received thereupon the name dihydrodesoxycodeine-A.

Dihydrodesoxycodeine-A also results from electrolytic reduction of desoxycodeine-A or the reduction of desoxycodeine-B with sodium and alcohol (11), but not from its catalytic hydrogenation as claimed by Freund (7), nor from electrolytic reduction of the amorphous so-called α-dihydrodesoxycodeine (see below).

Degradation of dihydrodesoxycodeine-A methiodide results in a crystalline methine base, des-N-methyldihydrodesoxycodeine-A, which can be hydrogenated, with addition of four hydrogen atoms to the same dihydro-des-N-methyltetrahydrodesoxycodeine as is obtained when two hydrogen atoms are added to des-N-methyltetrahydrodesoxycodeine (13). Dihydrodesoxycodeine-A methyl ether has also been degraded (1).

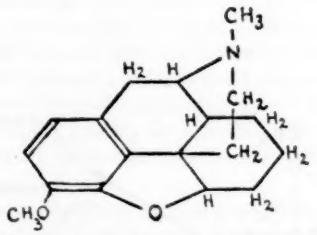
Dihydrodesoxycodeine-B (m. p. 128°) is a phenolic base formed by addition of two hydrogen atoms at the ether bridge in the nonphenolic

[85] In the preliminary investigation of Knorr and Hörlein (12) the compound was called desoxycodeine.

desoxycodeine-C (Formula VIII) when this substance is reduced by the electrolytic method. Dihydrodesoxycodeine-B adds one molecule of hydrogen in the presence of catalysts to give tetrahydrodesoxycodeine (11).

Dihydrodesoxycodeine-C (m. p. 111°) is prepared by electrolytic reduction of chlorodihydrocodide (p. 215). It is a phenol, and is probably formed through loss of hydrochloric acid from chlorodihydrocodide and reductive scission of the ether linkage (11). It was confused by Freund (7) with desoxycodeine-B (m. p. 119°). Through addition of one molecule of hydrogen by the catalytic method, dihydrodesoxycodeine-C is converted to tetrahydrodesoxycodeine (11).

Dihydrodesoxycodeine-D (m. p. 107°) is the only known nonphenolic dihydrodesoxycodeine. It was first described under the name dehydroxydihydrocodeine by Mannich (9), who obtained it by hydrogenation of β-chlorocodide with a palladium catalyst. It can also be prepared from reduction of α-chlorocodide in the presence of platinum (13), or by methylation of dihydrodesoxymorphine-D (14) (p. 149).



XI. Dihydrodesoxycodeine-D

Dihydrodesoxycodeine-D represents structurally the dihydro derivative of desoxycodeine-C, although it cannot be prepared from this substance, since hydrogenation of desoxycodeine-C always results in addition of four hydrogen atoms with scission of the ether linkage as explained above. Dihydrodesoxycodeine-D can be reduced electrolytically or with sodium and alcohol to tetrahydrodesoxycodeine (11). On heating with alkali, dihydrodesoxycodeine-D methiodide degrades to des-N-methyldihydrodesoxycodeine-D ("dehydroxydihydrocodomethine") (9).*

Dihydrodesoxycodeine-E (m. p. 139° to 140°), phenolic, was discovered by Speyer (15). It is prepared by electrolytic reduction of bromocodeinone (p. 295), a process which must involve reductive elimination of bromine, reduction of the keto group to a methylene group, and reductive scission of the ether ring. Dihydrodesoxycodeine-E is converted to tetrahydrodesoxycodeine by catalytic reduction.

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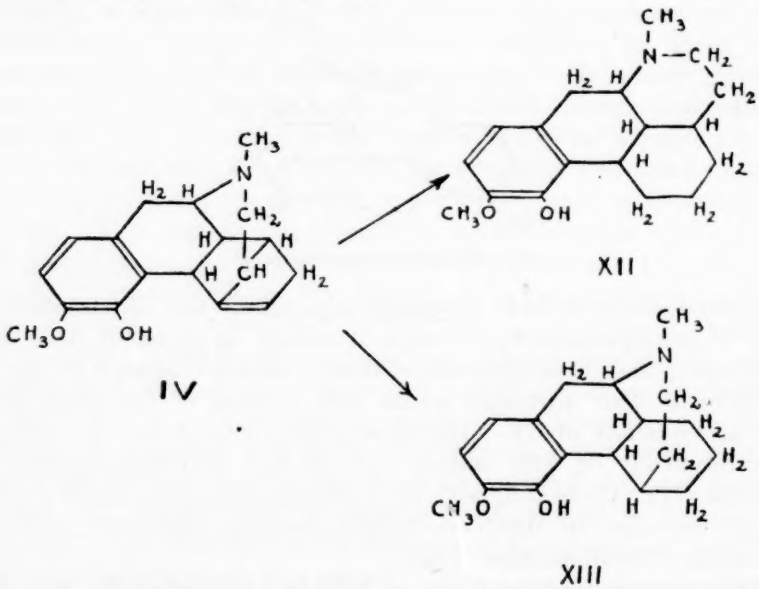
* See Appendix, p. 363.

Several substances have been erroneously described in the literature as dihydrodesoxycodeines. As mentioned above, the product of electrolytic reduction of α- or β-chlorocodide is not a dihydrodesoxycodeine as claimed (7) but is desoxycodeine-B. The dihydrodesoxycodeine of Knoll and Co. (8) is actually desoxycodeine-C. The α-dihydrodesoxycodeine described by Freund (7) proved to be a mixture containing traces of tetrahydrodesoxycodeine and of dihydrodesoxycodeine-D, but consisting in the main part of what appears to be a dimolecular reduction product, which forms a monomethiodide and a dimethiodide (13). The amorphous base is unaffected by electrolytic reduction (*cf.* Freund (7)).

Tetrahydrodesoxycodeine, $C_{18}H_{25}O_2N + \frac{1}{2}H_2O$, was first prepared by Freund (7) by catalytic reduction of desoxycodeine-A, and was named β-tetrahydrodesoxycodeine to distinguish it from the supposed α-tetrahydrodesoxycodeine. Since the latter has been shown to be actually a dihydrodesoxycodeine (-A), the Greek letter becomes superfluous (11).

The supposed isomeric tetrahydrodesoxycodeines were used by Freund as a support for his camphane-type codeine formula (p. 344). One of the isomers was regarded as resulting from a reductive rupture of the 5, 15-linkage, the other from the opening of the 8, 15-bond (7).

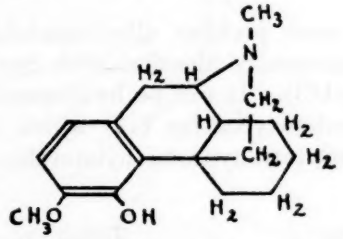


IV XII XIII

Similar arguments were used in favor of the bridge-ring formula advanced by Gulland and Robinson (16) in 1923. The overwhelming evidence in favor of a double linkage in the hydroaromatic ring of codeine necessitated a modification of this formula, and the supposed isomerism of α- and β-tetrahydrodesoxycodeines was attributed to stereochemical relationships on the asymmetric carbon atom at C-14. Cahn (18), in 1926, undertook an investigation of the two compounds, in which he showed that they were not identical, but did not demonstrate that they were actually isomers.

Tetrahydrodesoxycodeine is the end-product of reduction of all of the desoxy- and dihydrodesoxycodeines (diagram, p. 243), and is

likewise formed in varying amounts in the catalytic reduction of α- (13) or β-chlorocodides (13) (19). It is identical with the dehydroxytetrahydrocodeine which Mannich (9) obtained from catalytic reduction of β-chlorocodide and Clemmensen reduction of dihydrocodeinone (p. 249). Speyer's (20) dihydrothebacodine (p. 313) from electrolytic reduction of dihydrothebainone is probably the same as tetrahydrodesoxycodeine (13) (19) (21).*



XIV. Tetrahydrodesoxycodeine

Tetrahydrodesoxycodeine is an exceedingly stable substance. It distills or sublimes in a vacuum, yielding the anhydrous base, which may be obtained in two modifications of different melting point. Both of these forms, on recrystallization from dilute alcohol or acetone, give the hydrated base again (13).

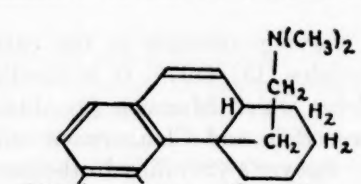
By demethylation with hydriodic acid, tetrahydrodesoxycodeine can be converted to the analogous tetrahydrodesoxymorphine. The two phenolic hydroxyl groups in this substance differ greatly in activity; only the hydroxyl in the 3-position is methylated by diazomethane, whereby tetrahydrodesoxycodeine is formed again (22).

The behavior of tetrahydrodesoxycodeine as a phenolic substance is remarkable, although not without analogy in morphine chemistry.[88] The crystallized base is practically insoluble in alkali; if dissolved in acid and precipitated with alkali the curdy precipitate does not dissolve appreciably in excess alkali. When, however, tetrahydrodesoxycodeine is dissolved in $\frac{1}{10}$ *N* hydrochloric acid and treated all at once with an excess of $\frac{1}{10}$ *N* alkali, only a momentary cloudiness appears which redissolves completely. Kondo (19) attributes the alkali-insolubility to the formation of an insoluble alkali salt, an explanation which is refuted by Small (13). The peculiar behavior is more probably attributable to a steric inaccessibility of the hydroxyl. It does not acetylate by the usual methods, and can only be methylated by the action of methyl iodide and alkali, which yields the methyl ether methiodide (7). Tetrahydrodesoxycodeine methyl ether has been prepared by distilling its methochloride in a vacuum (13).

The degradation of tetrahydrodesoxycodeine was first carried out by Freund (7) on the methyl ether; des-N-methylmethyltetrahydrodesoxycodeine (methyltetrahydrodesoxycodomethine) is an oily base whose methiodide loses trimethylamine with alkali to give an unidentified nitrogen-free product. The methiodide of tetrahydrodesoxycodeine itself also degrades smoothly to a methine base (XV),

*See Appendix, p. 363.

[88] The phenolic base dihydrothebainone (p. 309), for example, can not be extracted completely from ether into alkali (Schöpf, Ann. **452**, 247 (1927)).



XV. Des-N-Methyltetrahydrodesoxycodeine

which shows the same peculiar alkali-insolubility as the parent substance. It is apparently identical with Speyer's des-N-methyldihydrothebacodine (13). It can be hydrogenated to dihydro-des-N-methyltetrahydrodesoxycodeine (13) which agrees in properties with the dihydrodesoxytetrahydromethylmorphimethine of Cahn (23). (See p. 272.)

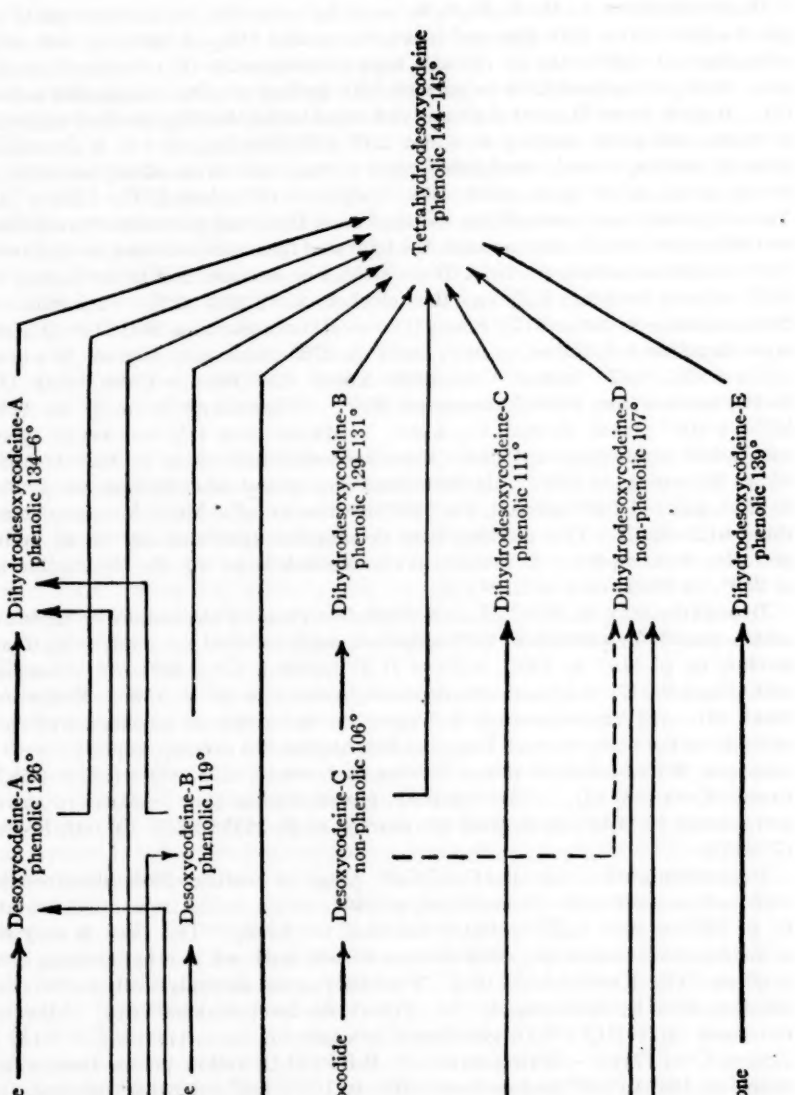
Tetrahydrodesoxycodeine → Des-N-methyltetrahydrodesoxycodeine → Dihydro-des-N-methyltetrahydrodesoxycodeine

Tetrahydro-α-methylmorphimethine → Chlorotetrahydro-α-methylmorphimethine → Desoxytetrahydromethylmorphimethine → Dihydro-des-N-methyltetrahydrodesoxycodeine

The desoxycodeines—tabular summary

Base	m. p.	$[\alpha]_D$	Hydrochloride	
			m. p.	$[\alpha]_D$
		Degrees		*Degrees*
Desoxycodeine-A	ca 122°	+118.1	ca 270°	+87
Desoxycodeine-B	119°	+71.3	unstable	
Desoxycodeine-C	106°	−197.4	114°	−132.7
Dihydrodesoxycodeine-A	134°–136°	−27.1	158°–160°	−41.4
Dihydrodesoxycodeine-B	128°–131°	−106.9	154°–160°	−76.4
Dihydrodesoxycodeine-C	109°–111°	−61.6	241°–242°	−3.6
			Acid Tartrate	
Dihydrodesoxycodeine-D	107°	−82.5	123°–125°	−39.6
Dihydrodesoxycodeine-E	139°	+58.1		
Tetrahydrodesoxycodeine	145°–147°	−32.1	262°	−23.5

Base	Hydriodide		Methiodide		Nature of base
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	
	Degrees	*Degrees*		*Degrees*	
Desoxycodeine-A	265				Phenolic.
Desoxycodeine-B	245	+38.3	oil		Do.
Desoxycodeine-C	160–165	−131.6	236°–240°		Nonphenolic.
Dihydrodesoxycodeine-A	242		250°–251°	−7.5	Phenolic.
Dihydrodesoxycodeine-B	255–256	−79.3	ca 175°		Do.
Dihydrodesoxycodeine-C	242–243	+52	245°–246°	+15.4	Do.
Dihydrodesoxycodeine-D	250		256°		Nonphenolic.
Dihydrodesoxycodeine-E			199°		Phenolic.
Tetrahydrodesoxycodeine	241	−24.2	263°	−33.3	Do.


α-Chlorocodide
β-Chlorocodide
Chlorodihydrocodide
Bromocodeinone
Desoxycodeine-A phenolic 126°
Desoxycodeine-B phenolic 119°
Desoxycodeine-C non-phenolic 106°
Dihydrodesoxycodeine-A phenolic 134–6°
Dihydrodesoxycodeine-B phenolic 129–131°
Dihydrodesoxycodeine-C phenolic 111°
Dihydrodesoxycodeine-D non-phenolic 107°
Dihydrodesoxycodeine-E phenolic 139°
Tetrahydrodesoxycodeine phenolic 144–145°

Descriptive Part (The Desoxycodeines and Derivatives)

DESOXYCODEINE-A: B=$C_{18}H_{21}O_2N$, prep. by reduction of α-chlorocodide or pseudochlorocodide with zinc and hydrochloric acid (12), or better by refluxing with zinc and alcohol (1) (5) (7), also from β-chlorocodide (6) or iodocodide (3); prep. from α-chlorocodide or iodocodide with methyl or ethyl magnesium iodide (3). It cryst. from dil. methyl alcohol in 6-sided leaflets holding one-half molecule of water, and melts unsharp at about 126° with foaming (1). It is soluble in alcohol, acetone, benzol, chloroform, ethyl acetate, and dilute alkali, insoluble in water; concd. alkali gives cryst. salts. $[\alpha]_D^{15}=+119°$ (alcohol, C=4.9215) (1). The anhydrous base is sometimes obtained from the usual preparative procedure, and when seed for it is once present, the hydrated form can no longer be prepared. The anhydrous form cryst. from dilute alcohol or acetone, and melts sharply at 157° without foaming; $[\alpha]_D^{24}=+119°$ (alcohol, C=2.268) (22). Reduction of desoxycodeine-A, Freund (7), Small (3). —HYDROCHLORIDE, B·HCl+C_2H_5OH, cryst. from alcohol, sinters at 165°, melts ca. 270° (decomp.); very sol. in water, $[\alpha]_D^{15}=+83°$, +87° (water, C=5.2285, 5.064) (1) (18). —HYDRIODIDE (1), B·HI, needles from water, decomp. ca. 265°. —BENZOATE (1), m. p. ca. 188°, $[\alpha]_D^{15}=+106°$ (absol. alcohol, C=5.53). —METHIODIDE (1), not cryst., gives with alkali a des-N-methyl base (Desoxycodomethine) of m. p. 162° to 164°, whose Nitrate m. at 202°. METHYLDESOXYCODEINE-A METHIODIDE, m. p. 251° to 252°, $[\alpha]_D^{15}=+108°$ (alcohol, C=2.29); it gives an oily Methyldesoxycodomethine with alkali. This methine base decomposes spontaneously to an amine and dimethylmorphol. ACETYLDESOXYCODEINE-A is an oil; its Hydriodide m. at 230°, its Methiodide at 270° (1).

DESOXYCODEINE-B: B=$C_{18}H_{21}O_2N+\frac{1}{2}H_2O$. Prep. by electrolytic reduction of α-chlorocodide in solution in 20% sulphuric acid; purified by cryst. from dilute alcohol, m. p. 119° to 120°, $[\alpha]_D^{22}=+71.3°$ (alcohol, C=3.617) (3). Compare with Freund's (7) supposed dihydrodesoxycodeine of m. p. 119°. Reduction, Small (3). —HYDROCHLORIDE, is formed by the action of alcoholic hydrogen chloride on the base; it cryst. from absolute alcohol but decomp. rapidly. —HYDRIODIDE, B·HI, yellowish-brown needles from water, m. p. 245°; $[\alpha]_D^{22}=+38.3°$ (water, C=1.698) (3). —METHIODIDE, not crystalline (3). —METHYL ETHER METHIODIDE (+H_2O), cryst. from dil. alcohol, m. p. 242° to 243° (3), (*cf.* Freund (7) 245°).

DESOXYCODEINE-C (3): B=$C_{18}H_{21}O_2N$, prep. by heating chlorodihydrocodide with sodium methylate in methanol at 140°; white cryst. from ethyl acetate, m. p. 105° to 106°, $[\alpha]_D^{20}=-199.4°$ (alcohol, C=1.745). The base is very sol. in methanol, ethanol, ether, chloroform or benzol, mod. sol. in ethyl acetate, insol. in alkali. (*Cf.* Knoll and Co. (8).) The base reduces electrolytically to Dihydrodesoxycodeine-B, catalytically to Tetrahydrodesoxycodeine (3). —HYDROCHLORIDE (3), B·HCl+H_2O, white cryst. from alcohol, m. p. 114°; $[\alpha]_D^{20}=-132.7°$ (water, C=1.771). —HYDRIODIDE (3), B·HI+H_2O, yellow prisms from water, sinters at 135° to 140° and melts at 160° to 165°; $[\alpha]_D^{19}=-131.6°$ (alcohol, C=1.401). —METHIODIDE (3), B·CH_3I, white cryst. from methanol, m. p. 236° to 240°. (*Cf.* Knoll and Co. (8) 136°.)

DIHYDRODESOXYCODEINE-A: B=$C_{18}H_{23}O_2N+\frac{1}{2}H_2O$, prep. by reduction of α-chlorocodide with sodium in boiling alcohol (1) (11), reduction of desoxycodeine-A or -B with sodium and alcohol (1) (11), or electrolytic reduction of desoxycodeine-A (11). From 1920 to 1931 the base was erroneously designated in the literature as α-tetrahydrodesoxycodeine. It seps. cryst. on addition of ammonia to solutions of the salts as chains of diamond-shaped plates and cryst. from dilute methanol or acetone. It sinters at 120° to 125°, m. at 134° to 136° with foaming; $[\alpha]_D^{22}=-27.1°$ (absol. alcohol, C=2.472) (11). (*Cf.* Knorr (1), Cahn (18).) The

base distills anhydrous in vacuo, and the anhydrous crystals (from petroleum ether) melt at 76° to 82°. It hydrogenates to tetrahydrodesoxycodeine (11). —HYDROCHLORIDE, B·HCl+C_2H_5OH, cryst. from alcohol, m. p. 158° to 160° with gas evolution; $[\alpha]_D^{22}=-41.4°$ (water, C=5.289) (11). *Cf.* Cahn (18), KNOTT (1). —HYDRIODIDE, prisms of m. p. 242° to 243° (18). —BENZOATE, m. p. 180°, $[\alpha]_D^{15}=-9°$ (water ?, C=5.145) (1). —METHIODIDE, B·CH_3I, white cryst. from water; it turns brown at 245° and m. at 250° to 251° (decomp.); $[\alpha]_D^{20}=-7.5°$ (alcohol, C=2.27). It degrades to a cryst. methine base (11). —METHYL ETHER METHIODIDE, cryst. from alcohol or water, m. p. 248° to 249°, $[\alpha]_D^{15}=-12°$ (99% alcohol). It yields an oily methine base on degradation (1).

DIHYDRODESOXYCODEINE-B: B=$C_{18}H_{23}O_2N+\frac{1}{2}H_2O$, prep. by electrolytic reduction of desoxycodeine-C: it cryst. in white flakes from dil. alcohol, m. p. 128° to 131°; $[\alpha]_D^{20}=-106.9°$ (alcohol, C=1.038), −69.1° (10% acetic acid, C=0.680). The base is soluble in most organic media and in alkali (11). It reduces to tetrahydrodesoxycodeine. —HYDROCHLORIDE (11), B·HCl, cryst. from absol. alcohol, m. p. 154° to 156° (decomp.); $[\alpha]_D^{21}=-76.4°$ (water, C=1.256). —HYDRIODIDE (11), B·HI, white needles from water, sinters at 244° and m. at 255° to 256°; $[\alpha]_D^{19}=-79.3°$ (alcohol, C=1.147). —METHIODIDE, B·CH_3I, white needles from water, m. p. ca. 175°.

DIHYDRODESOXYCODEINE-C: B=$C_{18}H_{23}O_2N+\frac{1}{2}H_2O$, prep. by electrolytic reduction of chlorodihydrocodide (11) (*cf.* Freund (7)). The base cryst. from dilute alcohol, m. p. 109° to 111°, $[\alpha]_D^{24}=-61.6°$ (alcohol, C=1.591). It is sol. in most organic media and in alkali; with catalytic hydrogen it reduces to tetrahydrodesoxycodeine (11). —HYDROCHLORIDE, B·HCl, white cryst. from absol. alcohol; sinters at 157°, m. at 241° to 242°; $[\alpha]_D^{20}=-3.6°$ (water, C=2.345) (11). —HYDRIODIDE, B·HI, white prisms from water, m. p. 242° to 243°, $[\alpha]_D^{22}=+52°$ (water, C=0.980). —METHIODIDE, B·CH_3I, white needles of m. p. 245° to 246°, $[\alpha]_D^{21}=+15.4°$ (alcohol, C=1.298).

DIHYDRODESOXYCODEINE-D, (Dehydroxydihydrocodeine (9)): B=$C_{18}H_{23}O_2N$, prep. by catalytic reduction of β-chlorocodide with colloidal palladium (9) (11), or of α-chlorocodide with platinum oxide (13), and separated from the tetrahydrodesoxycodeine through the acid tartrate. The base cryst. from ether in prisms of m. p. 107°, $[\alpha]_D^{20}=-82.5°$ (alcohol, C=0.866) (9) (11). It is very soluble in most organic media, insol. in alkali. With sodium and alcohol or by the electrolytic method it reduces to tetrahydrodesoxycodeine (11). —HYDRIODIDE, B·HI, yellow needles from water, m. p. 250° to 251° (decomp.). The hydrochloride does not crystallize (11). —ACID TARTRATE (11), B·$C_4H_6O_6$, white cryst. from water, m. p. 123° to 125°, $[\alpha]_D^{30}=-39.6°$ (water, C=1.793); it is soluble in 22 parts of water at 28°. —PICRATE (9), m. p. 207°. —METHIODIDE (9) (11), white prisms from alcohol, m. p. 256° to 257°; it degrades to a methine base, $C_{19}H_{25}O_2N$, rhombic cryst. from ether, m. p. 86°, whose Hydrochloride (+H_2O) m. at 222°, Picrate m. at 154°, and Methiodide m. at 238°.

DIHYDRODESOXYCODEINE-E: B=$C_{18}H_{23}O_2N+\frac{1}{2}C_2H_5OH$, prep. by electrol. reduction of bromocodeinone (15). It cryst. from absol. alcohol in prisms decomp. at 139° to 140°, $[\alpha]_D^{13}=+58.15°$ (dil. acetic acid, C=1.042); soluble in alkali. It reduces with catalytic hydrogen to tetrahydrodesoxycodeine (11) (15). —SALICYLATE, m. p. 198°. —METHIODIDE, m. p. 199°. —METHYL ETHER METHIODIDE, m. p. 245°. It degrades to a methine base, isolated as the Hydriodide, of m. p. 220°, and Methiodide of m. p. 103°; the end-product of degradation was not isolable (15).

DIHYDRODESOXYCODEINE of Knoll and Co. (8) is described above as Desoxycodeine-C.

DESOXYDIHYDROCODEINE of Knorr (1) is described as Dihydrodesoxycodeine-A.

α-DIHYDRODESOXYCODEINE of Freund (7), amorphous, is a dimolecular product which can be purified by high vacuum distillation and yields a cryst. mono- and di-methiodide (13).

TETRAHYDRODESOXYCODEINE (11): (β-Tetrahydrodesoxycodeine (7), dehydroxytetrahydrocodeine (9), dihydrothebacodine (20), thebainan (19)). B=$C_{18}H_{25}O_2N$ (+½H_2O), prep. by reduction of all of the desoxy- and dihydrodesoxycodeines, catalytic reduction of β-chlorocodide, Clemmensen reduction of dihydrocodeinone (9). The most suitable prep. method is catalytic reduction of desoxycodeine-A (7) or -B (11). It cryst. in 6-sided leaflets from dil. alcohol or acetone, and melts unsharp at 144° to 145° (147° to 148°); $[\alpha]_D^{25}=-32.1°$ (alcohol, C=1.712) (11). It is practically insol. in alkali. It distills or sublimes in vacuo to white crystals (anhydrous) of m. p. 124°, which change to a polymorphous form of m. p. 159° to 160°; both forms give the hydrated base when recryst. from dil. acetone (13). It demethylates with hydriodic acid to tetrahydrodesoxymorphine of m. p. 243° (22). —HYDROCHLORIDE, B·HCl+C_2H_5OH, m. p. 262° (7), white prisms from absol. alcohol-ether; $[\alpha]_D^{20}=-23.5°$ (water, C=2.509) (13). —HYDRIODIDE, B·HI+H_2O, m. p. 240° to 241° (7) (18); $[\alpha]_D^{19}=-24.2°$ (alcohol, C=2.360) (13). —METHIODIDE, B·CH_3I, cryst. from water, m. p. 263° (7); $[\alpha]_D^{26}=-33.3°$ (alcohol, C=1.80) (13). —METHYL ETHER, prep. by vacuum distillation of the methyl ether methochloride; it is a colorless oil, giving a cryst. Hydriodide, $C_{19}H_{28}O_2NI+H_2O$, yellow needles from water, m. p. 217° to 218°, $[\alpha]_D^{21}=-21.8°$ (alcohol, C=2.011) (13). TETRAHYDRODESOXYCODEINE METHYL ETHER METHIODIDE consists of white crystals of m. p. 256° to 257°, $[\alpha]_D^{21}=-3.54°$ (alcohol, C=1.691) (13). It degrades to an oily methine base whose Hydriodide m. at 175° to 185°, and Methiodide m. at 185° to 188°; further degradation products could not be isolated (7). TETRAHYDRODESOXYCODEINE METHYL ETHER METHOCHLORIDE, $C_{20}H_{30}O_2NCl$, cryst. from acetone, m. p. 255° to 256° (decomp.), $[\alpha]_D^{22}=-9.5°$ (water, C=2.63) (13).

BROMOTETRAHYDRODESOXYCODEINE: $C_{18}H_{24}O_2NBr+C_2H_5OH$, cryst. from alcohol, m. p. 135°. It reduces to tetrahydrodesoxycodeine by the electrolytic method (7).

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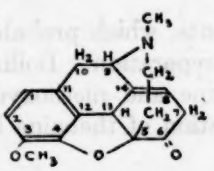
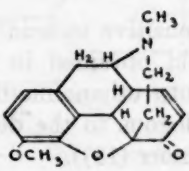
CODEINONE

Codeinone was first prepared by the controlled oxidation of codeine with potassium permanganate in acetone, or with chromic acid in 25% sulphuric acid at 50° to 60° (1). It is related to codeine as ketone to alcohol, and may be converted back to codeine by reduction.[87] The carbonyl group reacts to form an oxime (1) (3) (4) and a semicarbazone (5) in a normal way. Isocodeine, obtained from the hydrolysis of β-chlorocodide, may be oxidized to the same codeinone, showing that the isomerism of codeine and isocodeine lies in the relative positions of hydrogen and hydroxyl on the 6-carbon atom (3).

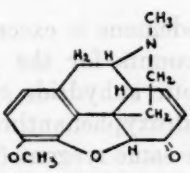
Codeinone is probably best represented structurally by one of the following formulas:[88]



I. Knorr-Hörlein

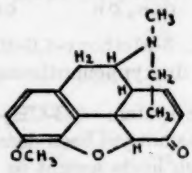


II. Wieland (6)

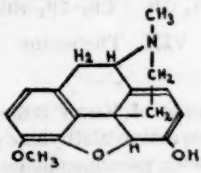


III. Gulland-Robinson (7)

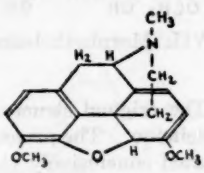
As Knorr pointed out (9), codeinone is the connecting link between codeine and thebaine; the latter may be regarded as the methyl ether of the enol (or other tautomeric (10)) form of codeinone:



III. Codeinone



IV. Hypothetical Enol Form



V. Thebaine

Indeed, thebaine can be converted directly to codeinone by boiling in dilute sulphuric acid (4), or by bromination of thebaine and reductive debromination of the resulting bromocodeinone (iron and sulphuric acid) (11);[89] see cut, p. 248. This is, in effect, a transformation of thebaine to codeine.

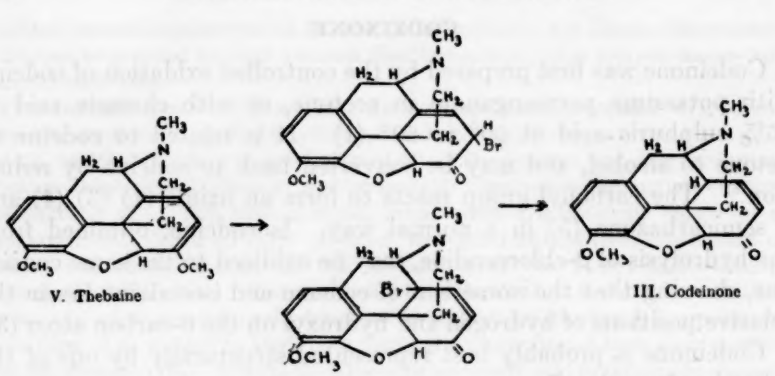
The relationship of codeinone to thebaine is further shown by its rearrangement products. Like thebaine, if heated with dilute hydrochloric acid, it forms thebenine; if fuming hydrochloric acid is employed, morphothebaine results (9).[90]

[87] No experimental data concerning this reduction are given in the literature; *cf.* Gulland and Robinson, J. Chem. Soc. **123**, 1001 (1923). It has been recently verified by Speyer and Hill. (See V. Braun and Cahn (2).) See Appendix, p. 363.

[88] *Cf.* also the bridge-ring formula of Freund and Speyer (8).

[89] When debromination is carried out with sodium hydrosulphite, an amorphous base results, which is suggested to be a dihydropseudocodeinone (12).

[90] A mechanism for this change is given by Schöpf and Borkowsky, Ann. **458**, 161 (1927). See MORPHOTHEBAINE, p. 329.

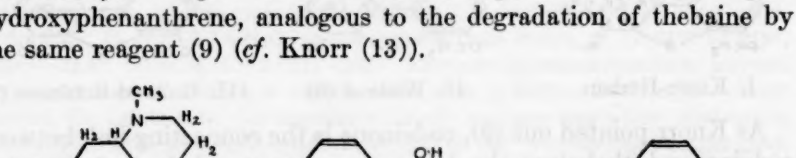


V. Thebaine

VI. Bromocodeinone

III. Codeinone

Codeinone is exceedingly sensitive to acid reagents, which probably accounts for the poor yield obtained in its preparation. Boiling acetic anhydride splits it into ethanolmethylamine and methoxydihydroxyphenanthrene, analogous to the degradation of thebaine by the same reagent (9) (*cf.* Knorr (13)).



VII. Morphothebaine

VIII. Thebenine

IX. 3-Methoxy-4,6-dihydroxyphenanthrene

The original structural formula of Knorr indicated the system -CO-CH_2- in codeinone. The presence of the active methylene group has not yet been demonstrated conclusively (14) (*cf.* with pseudocodeinone), which lends weight to the Robinson formula (Δ-7); Schöpf (15) postulates the possibility of rearrangement in acid media to the -CO-CH_2- form (Δ-8, 14). Compare the ring-chain tautomerism of Wieland (Ann. **444**, 82 (1925)); see also Schöpf (39).

Treatment of codeinone in concentrated hydrochloric acid with stannous chloride results in thebainone (16), which is obtained from thebaine itself under the same conditions (17). This change seems to involve a rearrangement of the nitrogen ring from 13 to 14 as well as the opening of the 4,5-ether ring with addition of two hydrogens; the double bond apparently occupies the 5,13-position. A mechanism for this change has been proposed by Schöpf (15) (see Thebainone).*

The extreme passivity of the carbonyl group in codeinone toward alkyl magnesium halides is remarkable. Prolonged treatment in ether solution is without effect (18); in isoamyl ether at 150° no reaction takes place, at 170° decomposition results.[91]

Codeinone is reduced with catalytic hydrogen to a dihydrocodeinone (19); this is probably identical with the dihydrocodeinone obtained

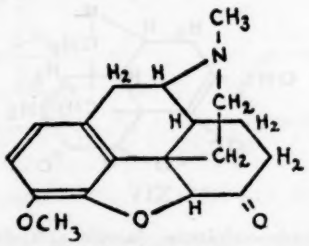
* See Appendix, p. 363.

[91] Unpublished observations, L. F. Small and Frank L. Cohen.

by hydrolysis of dihydrothebaine (20) (21) by catalytic reduction of bromocodeinone (22) or thebaine (23) or by treatment of codeine in strong acid with palladium and hydrogen at 60° to 90° (24) (25).[92]

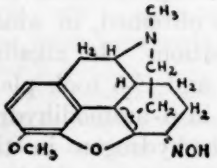
Merck (26) prepared dihydrocodeinone by chromic acid oxidation of dihydrocodeine; Freund (27), however, found the latter to be unaffected even by boiling chromic acid mixture (*cf.* Mannich (19), who states that permanganate oxidation failed).*

Dihydrocodeinone has been extensively investigated by Schöpf (28); it probably has the following formula:

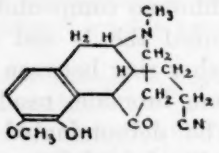


X. Dihydrocodeinone

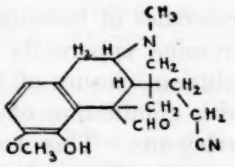
By subjecting the oxime of dihydrocodeinone to a Beckmann rearrangement, Schöpf (28) obtained a phenolic isoxime, proving that the ether bridge must be attached to 5 or 7; on steric grounds, the latter hardly comes into consideration. If the nitrogen ring is attached at 5 the isoxime must be a ketone (XII) if at 13, an aldehyde (XIII):



XI. Dihydrocodeinone oxime



XII. Isoxime



XIII. Isoxime

The isoxime itself unfortunately does not yield direct evidence on this point. In a circuitous but entirely logical way, Schöpf showed that the isoxime methyl ether must contain the aldehyde grouping, and the ethanamine chain is therefore not attached to carbon 5. Provided that no rearrangement has taken place,[93] this evidence applies also to dihydrocodeinone; for this substance, and hence for morphine, codeine, and thebaine, the point of linkage of the ethanamine chain is thereby fixed as C-13 (28).

Reduction of dihydrocodeinone by Clemmensen's method gives "dehydroxytetrahydrocodeine" (19), which proves to be identical with Freund's (27) β-tetra-

*See Appendix, page 364.

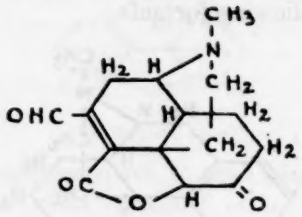
[92] Thebainone may likewise be regarded as a dihydrocodeinone; according to Schöpf, however, a deeper-seated change than mere opening of the ether bridge has taken place (15). (See p. 311.)

[93] The great stability of dihydrocodeinone, like other morphine derivatives hydrogenated in ring III, to acids, makes a shift of the nitrogen chain during the Beckmann rearrangement extremely improbable (28) (*cf.* Mannich and Löwenheim (19)).

hydrodesoxycodeine (29), (30) [94] (p. 241) and perhaps with Speyer's (31) dihydrothebacodine (29) (p. 313). Dihydrocodeine is also formed in small amounts in this reduction.

Sodium amalgam reduction of dihydrocodeinone gives dihydrothebainol (reductive opening of the ether bridge and conversion of the carbonyl to a secondary alcoholic group (29)).

Dihydrocodeinone is quite stable toward oxidation; hydrogen peroxide gives only an amine oxide (20). Ozonization results in opening the aromatic ring, with formation of an aldehyde, 6-ketodihydrocodinal (32), probably of the structure:



XIV

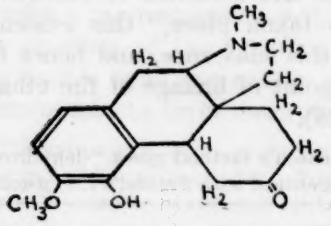
By acetylation of dihydrocodeinone (acetic anhydride), an acetyl group is introduced into ring III (33).

Dihydrocodeinone yields a well characterized condensation product with aminopiperonal (36).

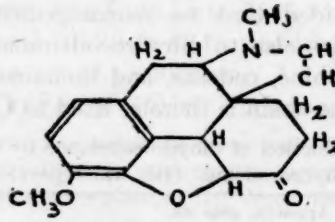
Dihydrohydroxycodeinone is discussed under Hydroxycodeinone, p. 254.

The preparation of dihydrocodeinone from dihydrothebainone by closure of the ether bridge has recently been accomplished by Schöpf and Pfeifer (40). By treatment of dihydrothebainone with two molecules of bromine a dibromo compound was obtained, in which bromine apparently occupied the 1- and 5-positions. In alkaline solution, closure of the ether ring between C-4 and C-5 took place with elimination of sodium bromide, resulting in 1-bromodihydrocodeinone. This could be debrominated with hydrogen in the presence of a catalyst, to dihydrocodeinone.

Using thebainol (Schöpf nomenclature, dihydrometathebainone) as the starting point, an isomer of dihydrocodeinone, which received the name dihydrometacodeinone, was prepared. It is represented by Schöpf as in Formula XVI.



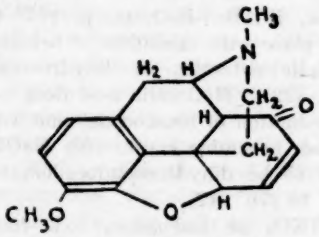
XV. Dihydrometathebainone



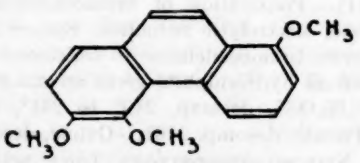
XVI. Dihydrometacodeinone

[94] Unpublished work of L. F. Small and F. L. Cohen.

Pseudocodeinone (34) (at first called isocodeinone (5)) is formed by oxidation of pseudocodeine (neoisocodeine of Schryver and Lees, J. Chem. Soc. **91**, 1408 (1907)) or of allopseudocodeine (β-isocodeine). Pseudocodeinone can be converted to 3, 4, 8-trimethoxyphenanthrene (5) (34), an isomer of the 3, 4, 6-trimethoxyphenanthrene obtained from codeinone. The carbonyl group must therefore be in the 8-position.



XVII. Pseudocodeinone



XVIII. 3, 4, 8-Trimethoxyphenanthrene

The change from codeine to pseudocodeine consists of a rearrangement or wandering of the hydroxyl group from the 6- to the 8-position. Allopseudocodeine is a stereoisomer of pseudocodeine, differing only in the relative positions of hydrogen and hydroxyl on the 8-carbon.*

In contrast to codeinone, pseudocodeinone gives reactions characteristic of the $CO\text{-}CH_2$- grouping; it forms an isonitroso derivative, and condenses readily with benzaldehyde (34). It reacts with diazonium salts, as does codeinone. This may, however, be interpreted as other than a reaction of an active methylene group (14). (*Cf.* for example, phenylazomorphine, p. 145.) The presence of a methylene group adjacent to the carbonyl is not in accord with the Robinson formula. (See p. 354.)

Both codeinone and pseudocodeinone, in the form of their methiodides, are split by heating with alcohol at 150° to 160° into trihydroxyphenanthrene derivatives and dimethylaminoethyl ethyl ether (5) (13) just as is thebaine methiodide (13). This instability is attributed to the unsaturated condition of ring III.

Pseudocodeinone is far more stable toward acids than codeinone; with acetic anhydride it degrades to form ethanolmethylamine and triacetylthebenine (5).

Pseudocodeinone reacts with ethyl mercaptan to form an addition product. This sulphethyl derivative apparently undergoes a scission of the ether linkage forming a phenol when treated with methyl iodide (38). This extraordinary reaction has a parallel in the behavior of β-ethylthiocodide with methyl iodide (p. 232)

Descriptive Part (Codeinone)

CODEINONE: B = $C_{18}H_{19}O_3N$, prep. by oxidation of codeine in acetone with $KMnO_4$, or in 16% sulphuric acid with $K_2Cr_2O_7$ at 50°. Purified from ethyl acetate; yield very poor (1). 20 g. of codeine in 80 g. water and 25 g. glacial acetic acid is treated with a sol. of 10 g. CrO_3 in 20 g. water. Warm on water bath to 50° until the oily ppt. dissolves; on cooling, a brown cryst. chromate seps. This is decomp. with NH_4OH, shaken out with ether, and the acetic mother liquor similarly treated. Recryst. from alcohol, 40% yield (35). May also be obtained by oxidation of methylcodeine (37). Other methods of preparation, Knorr (3) (4), Freund (11). It crystallizes in colorless prisms, becoming reddish

*See Appendix, page 364.

by action of light, m. p. 185° to 186°. Fairly soluble in methyl alcohol, benzene, chloroform, less so in alcohol or ethyl acetate, even less in ether or ligroin. Somewhat soluble in hot water. $[\alpha]_D^{15} = -205°$ (99% alcohol, C=1.007) (1). Codeinone is a strong skin irritant. —HYDROCHLORIDE, $B \cdot HCl + H_2O$, m. p. 179° to 180°. —PICRATE, from alcohol, m. p. 205°. —PICRONOLATE, m. p. 228°. —METHIODIDE, needles from water, $B \cdot CH_3I + 2H_2O$, m. p. 180° (1). —OXIME, $C_{18}H_{20}O_3N_2 + C_2H_5OH$, $[\alpha]_D^{15} = -499°$, (99% alcohol, C=0.1386); m. p. 212°; –Hydrochloride, m. p. 260° (1) (3) (4). —SEMICARBAZONE, m. p. 185° (5).

BROMOCODEINONE: $B = C_{18}H_{18}O_3NBr$, m. p. 156° to 157°. —HYDROCHLORIDE, $B \cdot HCl + 2H_2O$, m. p. 194°. —HYDROBROMIDE, $B \cdot HBr + H_2O$, m. p. 197° to 198°. —OXIME, $C_{18}H_{20}O_4N_2$, formation takes place with elimation of bromine (11). Preparation of bromocodeinone, catalytic reduction to dihydrocodeinone, electrolytic reduction, Speyer and Sarre (22). Hydriodic acid does not reduce bromocodeinone to codeinone (14). Reduction of bromocodeinone with sodium hydrosulphite gives an amorphous base, becoming cryst. with NaOH, $C_{18}H_{21}O_3N$, decomp. 240° to 241°, suggested to be dihydropseudocodeinone; –Picrate, decomp. 210°; –Oxime, decomp. 266° to 270° (12).

NITROSONORCODEINONE: from action of HNO_2 on codeinone, rods from absol. alcohol, m. p. 241° to 242°; insol. in alkali (29).

DIHYDROCODEINONE: (Dicodide) $B = C_{18}H_{21}O_3N$; preparation (19) (20) (21) (22) (23) (24) (25) (26). Three g. of dihydrothebaine is dissolved in 12 cc. conc. hydrochloric acid and boiled gently for three minutes (20); the crystalline base precip. from the cooled solution on addition of conc. ammonia; yield nearly quantitative. Cryst. from alcohol, m. p. 197° to 198°. —HYDROCHLORIDE, $B \cdot HCl + H_2O$ (20), (25), m. p. 82°, anhydrous, m. p. 125°, decomp. (19). —HYDRIODIDE, m. p. 219° to 220°. —METHIODIDE, m. p. 250° to 255°. —OXIME, m. p. 264°, whose Hydrochloride m. 63° (19). —PHENYLHYDRAZONE ($+C_2H_5OH$) m. p. 106° to 107°. —AMINE OXIDE (20). —BITARTRATE ($+2\frac{1}{2}H_2O$), m. p. 146° to 148° (25). NORCYANODIHYDROCODEINONE (20), from action BrCN, m. p. 224° to 225°. ACETYLDIHYDROCODEINONE, from action of acetic anhydride, m. p. 154° to 155°; –Hydrochloride, needles from water, decomp. 132° to 135° (33). n-BUTYRYLDIHYDROCODEINONE, is resinous, the Hydrobromide m. 225°, the Methiodide, rectang. plates from alcohol, froth at 125°, melt 220° (33). BENZOYLDIHYDROCODEINONE, is resinous, its Methiodide (from gl. acetic acid) decomp. 240° to 242° (33). ACETYLBROMODIHYDROCODEINONE, prisms from alcohol, m. p. 160° to 162°; its Hydrobromide (from water) m. 128° to 132° (33).

1-BROMODIHYDROCODEINONE (40); $C_{18}H_{20}O_3NBr$. Prep. by bromination of dihydrocodeinone in acetic acid; cryst. from alcohol in shining needles, m. p. 205° to 207°, insoluble in alkali. Prep. also by ring-closure from dihydrothebainone. Bromodihydrocodeinone debrominates (catalytic hydrogenation) to dihydrocodeinone. —HYDROBROMIDE, sinters 215°, m. at 217° to 218°.

1-CHLORODIHYDROCODEINONE (40): Prep. from dihydrocodeinone and chlorine-water at 0°; cryst. from methanol, m. p. 177° to 178°.

DES-N-METHYLDIHYDROCODEINONE: (Dihydrocodeinone methine), $C_{19}H_{23}O_3N$, prep. from dihydrocodeinone methiodide with hot alkali (20), or from hydrolysis of des-N-methyldihydrothebaine (6); cryst. from alcohol, m. p. 121° to 122°. The ether bridge is not opened by catalytic hydrogen; with aluminum amalgam des-N-methyldihydrothebainone is obtained. —METHIODIDE, m. p. 280° (284°); nitrogen-free degradation product not isolated. —OXIME, prisms from alcohol, m. p. 191° to 192.5°.

DIHYDRO-DES-N-METHYLDIHYDROCODEINONE (6): $C_{19}H_{25}O_3N$, prep. by cat. hydrogenation of des-N-methyldihydrocodeinone, from hydrolysis of dihydrodes-N-methyldihydrothebaine, or by oxidation of tetrahydromethylmorphimethine; colorless needles from ether, m. p. 110°. It is reduced by aluminum

amalgam to dihydro-des-N-methyldihydrothebainone. —OXIME, m. p. 183° to 185°, whose Hydrochloride m. 271° to 272°. —METHIODIDE, m. p. 295° to 298°.

DIHYDROCODEINONE ISOXIME (28): $C_{18}H_{22}O_3N_2$, by Beckmann rearrangement of the oxime, m. p. 196° to 198°. —PICRATE, prisms m. p. 207° to 208°. ACETYLDIHYDROCODEINONE ISOXIME PICRATE, decomp. 225°. DIHYDROCODEINONE ISOXIME OXIME, cryst. from alcohol, m. p. 218° to 219°. DIHYDROCODEINONE ISOXIME METHYL ETHER HYDRIODIDE, m. p. 249° to 250°. Degradation, see original.

DIANHYDRO-6-AMINOPIPERONALDIHYDROCODEINONE (36), from condensation with 6-aminopiperonal, m. p. 270° to 271°. —METHIODIDE, decomp. 260°.

6-KETO-DIHYDROCODINAL DISEMICARBAZONE: $C_{17}H_{23}O_4N_7$, from ozonization of dihydrocodeinone, spear-shaped cryst. decomp. 280° (32).

DIHYDROMETACODEINONE (41): $C_{18}H_{21}O_3N$, prep. from thebainol (dihydrometathebainone) by successive action of bromine and alkali, followed by debromination (catalytic hydrogen). Cryst. from methanol in needles of m. p. 196° to 201°. —OXIME, cryst. from methanol, m. p. 176° to 180°. In oxime preparation, thebainone oxime is obtained as a by-product; dihydrometacodeinone is very easily converted to thebainone by acids or alkalies.

1-BROMODIHYDROMETACODEINONE (41): $C_{18}H_{20}O_3NBr$, prep. from thebainol as described above. The base cryst. from alcohol-chloroform mixture, m. p. 241° to 246°.

PSEUDOCODEINONE: (Isocodeinone) (5), $B=C_{18}H_{19}O_3N$, from oxidation of pseudocodeine or allopseudocodeine (5) (34), m. p. 174° to 175°, recryst. from alcohol; $[\alpha]_D^{15}=-25°$ (99% alcohol, C=2.1125). —METHIODIDE, m. p. 220°. $[\alpha]_D^{15}=-12°$ (water, C=0.893); has been split to the methine base. —OXIME, amorphous. —SEMICARBAZONE, needles, m. p. 180° (5). BENZALPSEUDOCODEINONE, from condensation with benzaldehyde, oil, giving Methiodide, m. at 250°. ISONITROSOPSEUDOCODEINONE, yellow powder, decomp. 200° (34).

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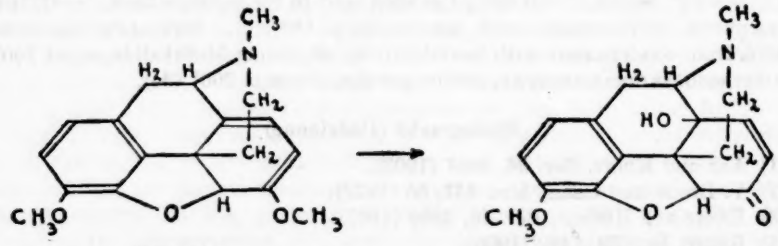
HYDROXYCODEINONE

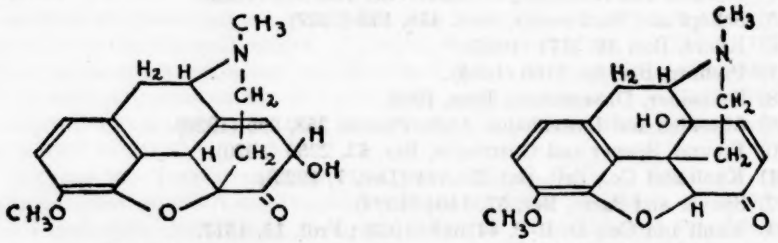
When thebaine is treated with hydrogen peroxide in acid solution, it apparently adds two hydroxyl groups. The methoxyl group in the hydroaromatic ring goes simultaneously to a keto group, by loss of methyl alcohol from the molecule (1).



Thebaine Hydroxycodeinone

The resulting hydroxycodeinone still contains the morphine skeleton essentially intact. The presence of an alcoholic hydroxyl, a double linkage, and a keto group can be demonstrated.

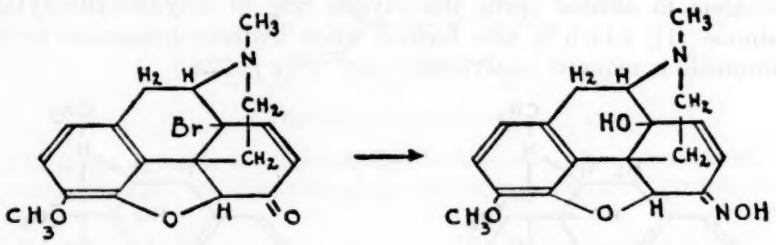
The formula tentatively proposed by Freund and Speyer (1) (I), represents hydroxycodeinone as an α-hydroxyketone, while the latest formula of Gulland and Robinson (2) (II) shows it as a γ-hydroxyketone.



I. Hydroxycodeinone II. Hydroxycodeinone

In support of II, Robinson advances the following considerations: The stability of the base toward alkaline cupric and silver solutions makes an α-hydroxyketone structure improbable. A β-hydroxyketone formula seems excluded in consideration of the difficulty of dehydrating hydroxycodeinone and its derivatives, and the impossibility of constructing a thebaine formula which can give rise to such a β-hydroxyketone in any plausible manner. These objections do not hold for the alternative proposed, that it is a γ-hydroxyketone. Hydroxycodeinone does not behave as though it contained the group —CO—CH_2—, but dihydrohydroxycodeinone does, facts which are best explained by assuming the system —CO—CH=C—C(OH)— in the former.

The position of the carbonyl group at C-6, and that of the ethanamine side chain, are undoubtedly the same as in codeinone, to which hydroxycodeinone is closely related. This relationship is evident in the preparation of hydroxycodeinone from bromocodeinone (p. 252) by the action of hydroxylamine (2) (3); substitution of bromine by hydroxyl takes place, resulting in hydroxycodeinone oxime:



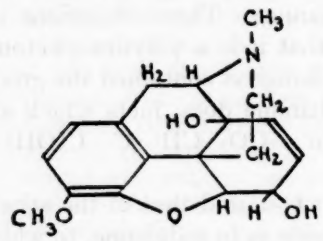
Bromocodeinone Hydroxycodeinone Oxime

Bromocodeinone is a derivative of codeinone, for it yields the latter on reduction (3), or dihydrocodeinone on catalytic hydrogenation (4).

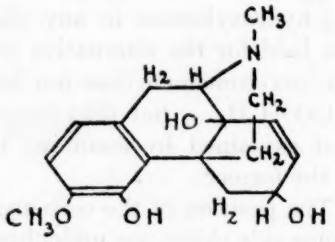
In agreement with Robinson, Schöpf (5) finds evidence for the location of the hydroxyl on C-14; if it were on C-9, C-10, C-15, or C-16, ring III would have the same degree of saturation as in codeinone, and hydroxycodeinone would be expected to show the same sensitiveness to acids. It is, on the contrary, stable toward 20% hydrochloric acid at 120° (1). On C-14, the hydroxyl is not in a position which permits it to be split out as water (5); it thus hinders ring III from becoming aromatic through loss of the ethanamine chain in degradation reactions, in accord with the Robinson (6) theory. A formula of the type of I, with a double bond in the β, γ-position to nitrogen (i. e. C-8-C-14) is, moreover, not in accord with the results of cyanogen bromide scission (1) (7).

The reduction products from hydroxycodeinone have proved to be particularly interesting. With acetic or formic acid and zinc dust it reduces to a hydroxycodeine which is described as 7-hydroxycodeine

by Freund (1) (8) and Speyer (9). It is an isomer of the hydroxycodeine of Ach and Knorr (10) (see p. 179) and on the basis of the Robinson formula for hydroxycodeinone will be here considered as 14-hydroxycodeine. At the same time, a phenolic compound, hydroxythebainol, is formed, which may likewise be prepared by electrolytic reduction of hydroxycodeinone (9).

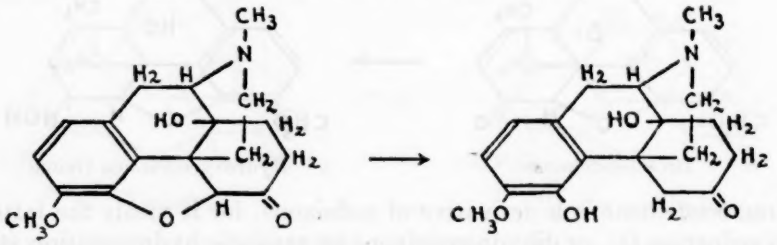


14-Hydroxycodeine



Hydroxythebainol

The action of catalytic hydrogen (1) or sodium hydrosulphite (11) gives dihydrohydroxycodeinone [95] by saturation of the double linkage; further reduction by the Clemmensen method, or with sodium amalgam in alcohol opens the oxygen ring to dihydrohydroxythebainone (1), which is also formed when hydroxythebainone or its dibromide is reduced catalytically (9). (See p. 258.)



Dihydrohydroxycodeinone

Dihydrohydroxythebainone

The reverse change has very recently been realized; dihydrohydroxythebainone reacts with two molecules of bromine to form a dibromo compound, which closes the 4, 5-ether linkage on treatment with alkali. The resulting 1-bromodihydrohydroxycodeinone can be debrominated to dihydrohydroxycodeinone (23).

Ochiai (14) (22) obtained from the Clemmensen reduction of dihydrohydroxycodeinone a dihydroxy compound which he names dihydrohydroxythebacodine. The fact that the hydroxyl of dihydrohydroxycodeinone was not replaced by hydrogen convinces Ochiai that it is not on C-7, favoring the Robinson conception.

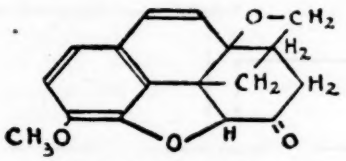
Catalytic reduction of hydroxycodeinone oxime in acid solution also results in dihydrohydroxycodeinone, while in alkaline solution dihydrohydroxythebainone is formed. This reaction points plainly

[95] This comes on the market as the hydrochloride under the trade name Eukodal (12) (13).

to the α, β-unsaturated ketone nature of hydroxycodeinone (9); comparative experiments show that the oximes of typical α, β-unsaturated ketones, as benzylideneacetone and dibenzylideneacetone, reduce under similar conditions to benzylacetone and dibenzylacetone respectively, with loss of ammonia, while dibenzylacetone oxime is unaffected (9).

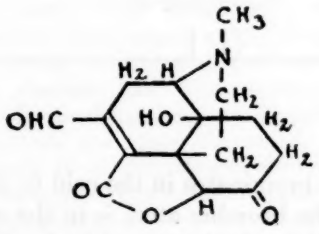
Hydroxycodeinone hydrazone reduces with palladium and hydrogen in aqueous acetone to dihydrohydroxycodeinone ketimine and dihydrohydroxycodeinone dimethylketazine, formed through condensation of the hydrazone with acetone. (15).

Dihydrohydroxycodeinone apparently exists in two tautomeric forms, which give the same salts (1). Because of the —CO—CH_2— group present, it condenses readily with aromatic aldehydes, as benzaldehyde, or piperonal (2). Exhaustive methylation leads to the nitrogen-free dihydrohydroxycodeone (1) in which a thebenol-type ring closure is believed to have taken place with the 14-hydroxyl (5). In the smooth course of this reaction, Schöpf (5) finds support for the location of the —OH on C-14 in hydroxycodeinone.

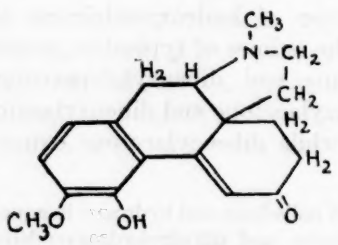


Dihydrohydroxycodeone

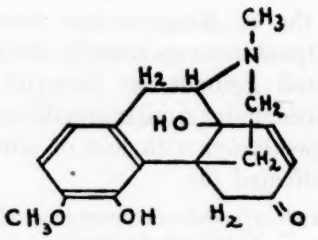
The action of ozone on dihydrohydroxycodeinone results in scission of the aromatic ring (16), with formation of the hydroxyketo analog of dihydrocodinal (p. 188).



By a third method of reduction, stannous chloride and concentrated hydrochloric acid, hydroxycodeinone is converted to hydroxythebainone (1) (9) (see p. 315) by reductive opening of the 4,5-oxygen bridge. Hydroxythebainone is thus formed from hydroxycodeinone by the action of the reagents used to prepare thebainone from codeinone. If the Schöpf formula for thebainone is correct, however, hydroxythebainone can not be a true thebainone derivative, since a shift of the ethanamine chain, as postulated for thebainone, to the occupied 14-position is in this case impossible.



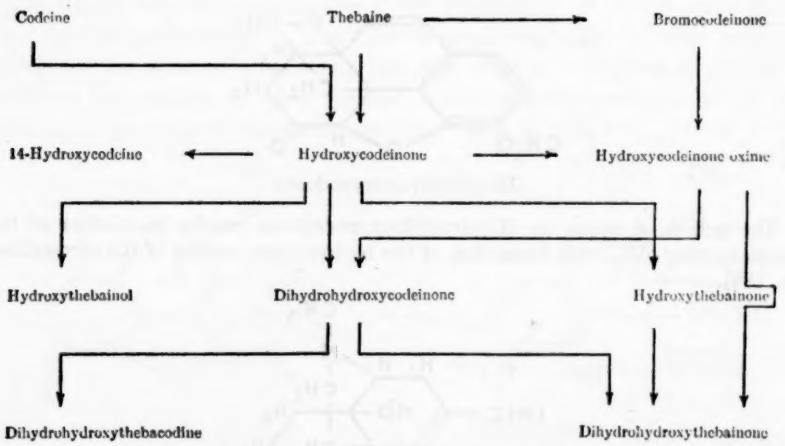
Thebainone (Schöpf)



Hydroxythebainone

Hydroxythebainone, as well as its dibromide or oxime, reduces with catalytic hydrogen to the dihydrohydroxythebainone already mentioned (9). When the latter is subjected to exhaustive methylation (in the form of its methyl ether), it gives the analog of dihydrohydroxycodeone, namely, methyldihydrohydroxythebaone (5).

The relationships of hydroxycodeinone are shown in the following diagram:



Hydroxycodeinone brominates in the cold to give a bromohydroxycodeinone in which the bromine atom is in the aromatic nucleus; the bromine is exchanged for hydrogen with simultaneous reduction of the 7,8-double bond (to dihydrohydroxycodeinone) on catalytic hydrogenation (17). By more energetic bromination, a dibromohydroxycodeinone is obtained, in which the second bromine may occupy the 8-position; this likewise debrominates with catalytic hydrogen to dihydrohydroxycodeinone (17).

Dihydrohydroxycodeinone yields a tribromo derivative, which may be converted to a trihydroxydihydrocodeinone by hydrolysis and reduction (17).*

Cyanogen bromide splits the methyl group from nitrogen of hydrooxycodeinone, with formation of cyanonorhydroxycodeinone (1); by

* See Appendix, p. 364.

hydrolysis, the CN– group is replaced by hydrogen, giving the secondary amine, norhydroxycodeinone (7). Acetyldihydrohydroxycodeinone behaves in a similar manner with cyanogen bromide (7). The N-methyl group of dihydrohydroxycodeinone is likewise split off by nitrous acid, resulting in nitrosonordihydrohydroxycodeinone (18).

Descriptive Part (Hydroxycodeinone)

HYDROXYCODEINONE (1) (19): B=$C_{18}H_{19}O_4N$; prep. by treatment of thebaine with 30% hydrogen peroxide in acetic acid, or with potassium dichromate and sulphuric acid. From codeine: 20 g. codeine in 80 g. water with 25 g. acetic acid is treated cold with a solution of 20 g. $Na_2Cr_2O_7$ in 25 g. water. An oily ppt. forms, which becomes cryst. after short warming. The mixture is heated to 80° with stirring until the solid goes into solution; the temperature rises spontaneously to 90°. After short standing, the base is precip. from the cold solution as the dichromate by adding excess of chromic acid solution. (Merck & Co. (20).) Cryst. from alcohol with a little chloroform, plates, decomp. 275°; sol. chloroform, ligroin, ethyl acetate, sparingly in alcohol, insol. in ether or water. Stable to strong acid or alkali. —HYDROCHLORIDE, B·HCl+H_2O, decomp. 285° to 286°; $[\alpha]_D^{20}=-149.7°$ (water, C=2.502). —OXIME (1) (3) decomp. 279° to 280°; Acetyl deriv. m. p. 214°· (decomp.). —OXIDE (1) (17), from further treatment of hydroxycodeinone with H_2O_2; needles, decomp. 243°; Picrate, m. p. 187° to 188°; Sulphonic acids, decomp. 260° and 270°. —SULPHONIC ACID: $C_{18}H_{18}O_4N\cdot SO_3H$, decomp. 210°. —METHIODIDE (1), decomp. 247°, giving an amorphous des-N-methyl base, whose Methiodide m. 267° (decomp.). —HYDRAZONE (15), m. p. 221° to 222°, gives by reduction a Ketimine, m. p. 216° to 217°.

ACETYLHYDROXYCODEINONE (1), by action of acetic anhydride, m. p. 185°; Hydrochloride, 258°; Oxime (+H_2O) m. p. 148°. BENZOYLHYDROXYCODEINONE (1), m. p. 245° to 247°; crystalline Hydrochloride. BROMOHYDROXYCODEINONE (17), needles, m. p. 204° to 205°, $[\alpha]_D^{13}=-80.21°$ (acetic acid, C=1.037); Hydrobromide, decomp. 280°; Acetyl deriv., m. p. 238°; Phenylhydrazone, decomp. 250°. DIBROMOHYDROXYCODEINONE (17), m. p. 194° to 195°, $[\alpha]_D^{13}=-120.4°$ (acetic acid, C=1.008); Hydrobromide, m. p. 265°; Acetyl deriv., m. p. 219°; Phenylhydrazone, decomp. 238°. CYANONORHYDROXYCODEINONE (1), action of CNBr on acetylhydroxycodeinone, m. p. 255°, gives OXIME. NORHYDROXYCODEINONE (7), from the cyano compound, m. p. 218° (decomp.), $[\alpha]_D^{13}=-123.33°$ (acetic acid, C=0.914); Hydrobromide; Nitroso deriv., m. p. 234°; Allyl deriv., an oil whose Hydriodide, m. 192°. HYDROXYCODEINONE DIMETHYLKETAZINE (15), m. p. 171°.

DIHYDROHYDROXYCODEINONE: B=$C_{18}H_{21}O_4N$, from catalytic reduction of hydroxycodeinone (1) (8) (21), its oxime (9), or its bromination products (17), or reduction of hydroxycodeinone with sodium hydrosulphite (11); m. p. 218° to 220° (from alcohol). Readily sol. in alcohol or chloroform, nearly insol. in ether or water. Does not reduce ammoniacal silver or Fehling's solution. Tautomeric form, m. p. 219° to 220°, differs in crystal form and solubility (1). —HYDROCHLORIDE, m. p. 268° to 270°, cryst. from water or dil. alcohol. $[\alpha]_D^{20}=-125.2°$ (water, C=2.527). —HYDRIODIDE, m. p. 189° to 190°. —OXIME, Hydrochloride, decomp. 275° to 278°. —PHENYLHYDRAZONE (1), m. p. 204°. —HYDRAZONE, leaflets, m. p. 213° to 214° (15). —METHIODIDE (1), decomp. 251°; gives a des-N-methyl base of m. p. 115° (Oxime, 185° to 186°) whose Methiodide, m. p. 255° to 256°, decomp. with alkali to Dihydrohydroxycodeone, $C_{17}H_{16}O_4$, m. p. 214° to 215°, $[\alpha]_D^{20}=-140.8°$ ($CHCl_3$, C=1.763) (1) (9). The last-named hydrogenates to Tetrahydrohydroxycodeone, m. p. 150° to 153°,

obtained also from decomp. of dihydro-des-N-methyldihydrohydroxycodeinone methiodide (m. p. 280°, corresponding base m. p. 136° to 137°) (5). DIHYDROHYDROXYCODEINONE METHIODIDE OXIME HYDROCHLORIDE, decomp. 275° to 278°. ACETYLDIHYDROHYDROXYCODEINONE (1), m. p. 215° to 216° (alcohol), giving an Oxime hydrochloride, m. p. 179° to 180°. BENZOYLDIHYDROHYDROXYCODEINONE, m. p. 275° to 276°. BROMODIHYDROHYDROXYCODEINONE (17) (23), leaflets (alcohol), m. p. 182°; Hydrobromide, needles decomp. 227° to 230°, $[\alpha]_D^{13} = -93.15°$ (water, C=1.015); Acetyl deriv. (alcohol), m. p. 217°; Semicarbazone, decomp. 249°. TRIBROMODIHYDROHYDROXYCODEINONE, from bromination in boiling acetic acid. Prisms (acetone), decomp. 228°, $[\alpha]_D^{13} = -225.56°$ (acetic acid, C=1.015); Hydrobromide, decomp. 255°; Acetyl deriv., decomp. 220°. TRIHYDROXYBROMODIHYDROCODEINONE, from NaOH on the tribromo compound, leaflets decomp. 302°; Monoacetyl deriv., decomp. 267° TRIHYDROXYDIHYDROCODEINONE, by debromination (Pd–H_2) of the trihydroxybromo compound, prisms, decomp. 320°.

DIHYDROHYDROXYCODEINONE DIMETHYLKETAZINE (15) m. p. 159°.

CYANONORDIHYDROHYDROXYCODEINONE (7), Acetyl deriv., decomp. 256°.

NORDIHYDROHYDROXYCODEINONE, from hydrolysis of the cyanonor compound, an oil; Hydriodide, decomp. 295°, $[\alpha]_D^{13} = -114.54°$ (C=1.004); Nitroso deriv. (alcohol), decomp. 259° (18). Base gives an Allyl deriv. not cryst.; Hydrobromide, decomp. 182°. PIPERONYLIDENEDIHYDROHYDROXYCODEINONE (2) yellow amorphous powder. DIANHYDRO-6-AMINOPIPERONALDIHYDROHYDROXYCODEINONE, prisms, m. p. 282° to 283° (2).

DIHYDROHYDROXYTHEBACODINE (14) (22): $C_{18}H_{25}O_3N$, from Clemmensen reduction of dihydrohydroxycodeinone; prisms of m. p. 138° to 139°, $[\alpha]_D^{25} = -58.18°$; practically insoluble in KOH, contains one OCH_3, and two OH groups.

14-HYDROXYCODEINE is described under Hydroxycodeine, page 194.

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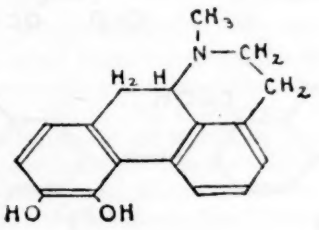
(21) Freund, U. S. Pat. 1485673 (March 4, 1924).
(22) Kondo and Ochiai, Ann. **470,** 224 (1929).
(23) Schöpf and Perrey, Ann. **483,** 159 (1930).

APOMORPHINE [96]

This base results from a deep-seated rearrangement which takes place in the morphine nucleus through vigorous action of a number of acidic reagents. The researches of Pschorr have shown it to be a derivative of isoquinoline as well as of phenanthrene. represented by the formula:



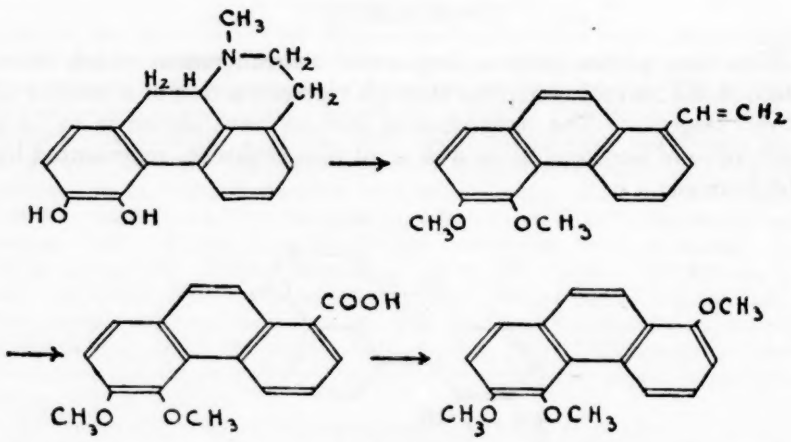
Apomorphine

By the action of sulphuric acid on morphine, Arppe (2) (1845) obtained an amorphous substance which seems to have been apomorphine sulphate. It was further investigated by Laurent and Gerhardt (3), who showed that it corresponded to morphine sulphate less one molecule of water ("sulphomorphide"). The free base was prepared by Matthiessen and Wright (4) from morphine with 35% hydrochloric acid at 140° to 150° (phosphoric acid, Wright (1)). It is also formed when morphine is heated with zinc chloride solution (5) (6), or from codeine (7) or chlorocodide (8) with concentrated hydrochloric acid. Fulton (9) describes a crystalline compound resembling apomorphine, obtained by the action of concentrated sulphuric acid on morphine at 40° *.

The amorphous nature of apomorphine, and its high oxidability delayed for many years its chemical study, although its valuable physiological action was early recognized (4). Mayer and Wright (10) examined without result the oxidation products; from destructive distillation of apomorphine hydrochloride they were able to isolate pyridine. Herzig and Meyer (11) showed the presence of an N-methyl group.

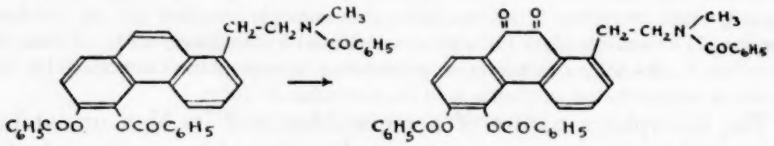
Pschorr, Jaeckel, and Fecht (12) first obtained apomorphine in the crystalline form. The presence of two hydroxyl groups was shown by formation of a dibenzoyl derivative with benzoyl chloride (*cf.* Danckwortt (13)). By more vigorous benzoylation the nitrogen ring was opened to give a nonbasic tribenzoyl compound. By exhaustive methylation a dimethoxyvinylphenanthrene was obtained, which oxidized to 3,4-dimethoxyphenanthrene-8-carboxylic acid (12) (14). This was identified by conversion (15) to the synthetic 3,4,8-trimethoxyphenanthrene (16).

*See Appendix, p. 365.
[96] The prefix APO-, lacking in the elements of water, Wright (1).



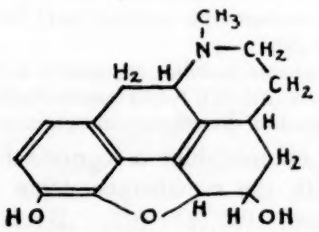
Assuming that the N-atom is attached to the 9-carbon atom (17) as in morphine (18), the two extra hydrogen atoms must occupy positions 9 and 10 (as shown by the course of exhaustive methylation).

The oxidation of tribenzoylapomorphine to a 9, 10-phenanthrenequinone gave additional evidence that the nitrogen-containing side chain is not attached through carbon in either of these positions (19):



Similar evidence was obtained through zinc dust distillation of the before-mentioned dimethoxyvinylphenanthrene, which resulted in isomeric ethylphenanthrenes. A comparison of these with synthetic 9 (or 10) ethylphenanthrenes showed the ethyl group not to be in these positions (14).

The apomorphine researches had an important bearing on the oxazine formula for morphine. Since apomorphine contains no indifferent (ether) oxygen, but still has the nitrogen in a ring structure, it became necessary to assume that the oxazine ring broke at the ether oxygen and reestablished a bond to carbon, or that the indifferent oxygen of morphine did not form a part of the nitrogen ring. Evidence for the latter hypothesis existed already in the degradation of thebainone (20), and in the fact that Vongerichten's (21) morphenol was known to contain the indifferent oxygen in a 4,5-ether linkage. The proof of a pyridine ring in apomorphine was advanced by Pschorr (17) (not without reservations) as support for his pyridine formula for morphine, which was shortly to fall through the work on the isomeric codeinones (22).

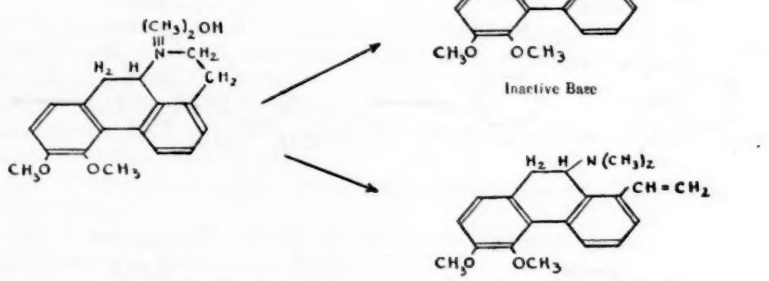


Morphine (Pschorr, 1902–1907)

The action of concentrated hydrochloric acid on morphine, as employed in apomorphine preparation, results first in the formation of β-chloromorphide (23). (*Cf.* Boehringer and Sohn (24).) This is converted to apomorphine by more vigorous action of hydrochloric acid (*cf.* Matthiessen and Wright (8)) and probably plays an important part in the reaction mechanism.

Apomorphine, as a tetrahydroisoquinoline derivative, suffers ring scission with cyanogen bromide, instead of the demethylation which is characteristic of true morphine derivatives with this agent (25).

It was found by Gadamer (26) that the Hofmann degradation of apomorphine proceeds in two ways, giving the optically inactive methine base of Pschorr, and an optically active base, $[\alpha]_D = +138.6°$.



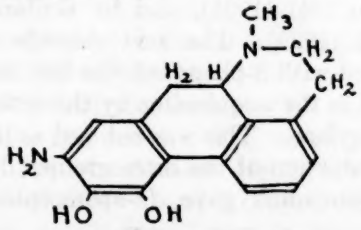
Inactive Base

Active Base

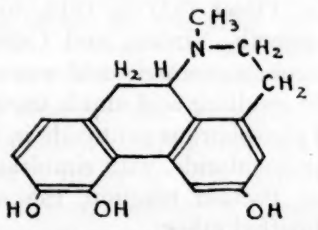
The Emde degradation (Faltis and Krauss (27)) results in only one (inactive) dihydrodimethylapomorphimethine.

Apomorphine yields with concentrated sulphuric acid a crystalline sulphonic acid, in which the sulphonic residue is assumed to be on C-1. It probably possesses an inner salt structure like that of sulphanilic acid (63).

Very few morphine derivatives undergo the rearrangement to apomorphine types; 2-nitroso- and 2-amino-morphine yield by the action of hydrochloric acid the corresponding substituted apomorphines (28). Morphothebaine, which already contains the apomorphine skeleton, may be demethylated to give 6-hydroxyapomorphine (29).



2-Aminoapomorphine



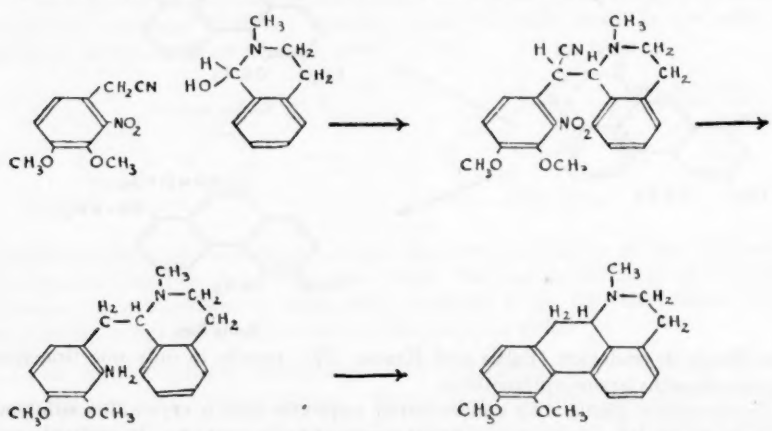
6-Hydroxyapomorphine

2-Phenylazomorphine, in contact with sulphuric acid for one week, rearranges to 2-phenylazoapomorphine (30).

The alkaloids from *Stephania japonica* apparently belong to the apomorphine group. Kondo and Sanada (31) (32) found desoxydihydroepistephanine methiodide to be the optical antipode of dimethylapomorphine methiodide.

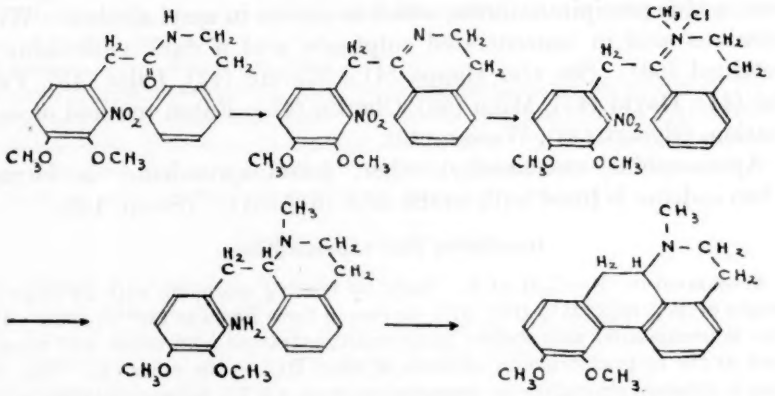
By methylation of apomorphine a monomethyl ether is obtained, which is identical with the pseudoapocodeine prepared by melting codeine with oxalic acid (12) (61) (62). By further methylation, a dimethyl ether is formed (62), which has assumed importance because of the syntheses described below.

The synthesis of apomorphine (in the form of its dimethyl ether) was accomplished independently by Pschorr and Avenarius (33), and by Späth and Hromatka (34) in 1928. The first-named investigators proceeded from vic. 3,4-dimethoxy-2-nitrobenzylcyanide and α-hydroxy-N-methyltetrahydroisoquinoline. These were condensed by the action of sodium ethylate. By hydrolysis of the CN– group and elimination of carbon dioxide, followed by reduction of the nitro group, an amine was obtained which could be converted by the Pschorr phenanthrene ring closure to apomorphine dimethyl ether.



Identification was made through the methiodide and the methine base derived from it.

The synthesis of Späth and Hromatka was based on the Bischler-Napieralski isoquinoline synthesis, followed by a phenanthrene ring closure. This plan had already been tried without success by Kay and Pictet (35) in 1913, by Kondo (36) (1925), and by Gulland, Haworth, Virden, and Callow (37) (1929). The acid chloride of nitrohomoveratric acid was condensed with β-phenylethylamine, and the resulting acid amide transformed to the isoquinoline by the action of phosphorous pentoxide in boiling xylene. This was reduced as the methochloride, with simultaneous reduction of the nitro group. By the Pschorr reaction, the amino compound gave *d,l*-apomorphine dimethyl ether:



All attempts to racemize *l*-apomorphine dimethyl ether for comparison failed; the synthetic product gives, however, with benzoyl chloride the same benzoylation product as the *l*-isomer (the asymmetry of the 9-carbon atom being destroyed when the N-ring opens.)

The following apomorphine reactions are described by Beckers (38):

Reagent and procedure	*Effect*
10% $FeCl_3$ solution	Blue color, sensitive 1:9999.
Shake up aqueous solution with $CHCl_3$, add NaOH, shake with air.	Aqueous layer, red-violet, $CHCl_3$, blue.
Beckurt's reagent (1/10 *N* $KMnO_4$)	Green.
Johannson's reagent (1 g. ammonium vanadate in 100 c.c. conc. H_2SO_4.)	Magnificent blue.
Linke's (Marquis') reagent, (Formaldehyde-H_2SO_4).	Violet→rose-red→blue-black.
Manseau's reagent (5% solution of hexamethylenetetramine in conc. H_2SO_4).	Intense brown-violet.
Bedson's test, boil with KOH	Brown.
Marmé's reagent (ammonium molybdate in conc. H_2SO_4).	Blue.
Mecke's reagent (1 g. selenic acid in 200 g. conc. H_2SO_4).	Dark violet.
Orlow-Horst's reagent (ammonium persulphate in H_2SO_4).	Green→blue.
Wangerin's reagent (0.3 g. uranium acetate +0.3 g. sodium acetate in 100 c.c. water).	Brown ppt., dissolves colorless in acids, repptd. by alkalies.
Feinberg's test: few drops of 1% $K_3Fe(CN)_6$ solution, 1 c.c. benzene, shake.	Benzene colored violet-red; addition of Na_2CO_3 turns it to violet. Test not obtainable in presence of acids. (*Cf.* Van Itallie (39).)
Becker's reaction: base or salt in aqueous solution, add $NaNO_2$, then HCl.	Blood-red color. Can be carried out in presence of morphine.

Grimbert and Leclère (40) describe a sensitive test for apomorphine: if a solution of apomorphine salt is boiled a few seconds with 5 drops of saturated $HgCl_2$ solution and 5 drops of 10% sodium acetate solution, and extracted with amyl alcohol, the latter is colored blue; sensitive to 1 part in 500,000. If much apomorphine is pre-

sent, a blue precipitate forms, which is soluble in amyl alcohol. With selenious acid in concentrated sulphuric acid a dark violet-blue is obtained (50). See also Heppe (41), Marmé (42), Palet (43), Paolini (44), David (45), Miko (46), Oberlin (47); Eaton method of estimation, Glycart (48), Warren (49).

Apomorphine monomethyl ether, pseudoapocodeine, is formed when codeine is fused with oxalic acid (61) (64). (See p. 183).

Descriptive Part (Apomorphine)

APOMORPHINE: B=$C_{17}H_{17}O_2N$. Prep. by heating morphine with 10 times its weight of 35% HCl (25% HCl (51)) for two to three hours at 140° to 150°. The base is precipitated with sodium bicarbonate, extracted with ether, and crystallized as the hydrochloride on addition of conc. HCl to the ether (4). The free base is obtained crystalline by precipitation from a 2.5% aqueous solution of the hydrochloride, extracting with ether and concentrating after drying over K_2CO_3; all operations performed in the absence of oxygen (12). It is soluble in alcohol, acetone or chloroform, sparingly sol. in ether or benzol, insol. in ligroin, slightly sol. in water; cryst. with one molecule of ether. It oxidizes rapidly in the air, and in alkaline solution absorbs oxygen like pyrogallol (10). Apomorphine sublimes crystalline in vacuum (52). The absorption in the ultra-violet has been studied by Gompel and Henri (53).

—HYDROCHLORIDE: B·HCl, prisms from water; cryst. measurements, Miller (54). $[\alpha]_i^{16}=-30.5°$ (water, p=2.056) (12). —SULPHATE, $n_D=1.70, 1.66$ (55). —SILICOTUNGSTATE, buff-colored compound (56). —METHOCHLORIDE, cryst. from alcohol, m. p. 205° to 210° (57) (58). —METHOBROMIDE (Eupophin), needles from methanol or acetone, cryst. with solvent, m. p. 180° (57) (58) (59). —METHONITRATE, colorless leaflets from alc.-acetone mixture (57) (58). —METHOMETHYLSULPHITE (59).

DIBENZOYL—, colorless prisms from alcohol, m. p. 156° to 158°. $[\alpha]_i^{17}=+43.44°$ ($CHCl_3$, p=3.329); gives a Methiodide of m. p. 229° to 230°. DIBENZOYLACETYL—, m. p. 156° to 158°. TRIBENZOYL—, needles from $CHCl_3$, m. p. 217° to 218° (corr.), oxidizes with CrO_3 to the Quinone, of m. p. 178° to 179°, yellow cryst. whose Phenylhydrazone m. 235° to 236° (12).

DIACETYL—, m. p. 129°, $[\alpha]_D=-67.26°$ (dil. HCl), giving a Methiodide, m. p. 233°, $[\alpha]_D=-47.2°$ (acetic anhydride). TRIACETYL—, m. p. 137° (60).

—METHYL ETHER (Pseudoapocodeine), from melting codeine with oxalic acid, or from methylation of apomorphine (12) (61) (62), cryst. from alcohol, m. p. 105° to 110°, $[\alpha]_D^{15}=-90°$ (absol. alcohol, C=0.84); forms a Methiodide, decomp. 230° to 233°, $[\alpha]_D^{15}=-17°$ (methanol, C=1.208); -Hydriodide, m. p. 288°; Diacetyl derivative ($+H_2O$), m. p. 130°. METHYLACETYLAPOMORPHINE METHIODIDE, m. p. 241° to 242°, $[\alpha]_D^{15}=-39°$ (water, C=1.578).

—DIMETHYL ETHER (62), liquid, $[\alpha]_D^{15}=-148°$ (absol. alcohol, C=1.639). Its Hydriodide m. about 220°, $[\alpha]_D^{15}=-49°$ (absol. alcohol, C=1.379); the Methiodide melts 195°, $[\alpha]_D^{15}=-46°$ (absol. alcohol, C=2.696). The *d*-Bitartrate m. 177° to 178° (34). BENZOYLDIMETHYLAPOMORPHINE melts 165.5° (34).

DIMETHYLAPOMORPHIMETHINE, from degradation of dimethylapomorphine methiodide; the Hydrochloride m. 220° to 221° (corr.); -Methiodide, m. 242° to 244° (corr.), degrades to 3, 4-dimethoxy-8-vinylphenanthrene (12) (14) (33). DIHYDRODIMETHYLAPOMORPHIMETHINE (27) is formed from the Emde reaction with dimethylapomorphine methochloride; the base cryst. in leaflets, m. p. 70.5° to 71.5°; -Methiodide, m. p. 240°.

2-NITROSO— (28), from 2-nitroso morphine with HCl at 145°; red needles from absol. alcohol, m. p. above 300°. The Hydrochloride decomp. above 200°.

2-AMINO— (28), from aminomorphine; amorphous, gives a cryst. Hydrochloride, m. p. 260° to 265°.

2-PHENYLAZO— (30), not fused at 310°.

HYDROXYAPOMORPHINE (29), prep. from morphothebaine with HBr at 170°, isolated as hydrobromide $C_{17}H_{17}O_3N \cdot HBr$, needles from water, m. p. 261° to 262°.

APOMORPHINE SULPHONIC ACID, $C_{17}H_{17}O_5NS$, prep. by treatment of apomorphine with conc. sulphuric acid at 0°; colorless needles, melting above 300°; sol. with diff. in water or organic solvents, sol. in soda or alkalies (63).

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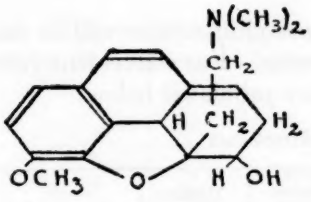
THE METHYLMORPHIMETHINES

The products resulting from the opening of the nitrogen ring of codeine and its isomers by the exhaustive methylation method of A. W. Hofmann have played an important part in the determination of the structure of these bases and hence of that of morphine. The nature of the process makes its application to morphine itself difficult, since the reaction is complicated (1) by the tendency of the quaternary base to form a phenol-betaine (2) with the phenolic hydroxyl.

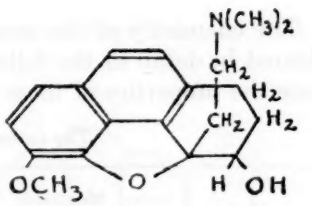
Grimaux (3), (4), in 1882, obtained "méthocodéine" by boiling codeine methiodide with silver oxide (*cf.* How's (5) experiments, 1853). Hesse (1), a year later, prepared the same product, which he named methylmorphimethine (now called α-methylmorphimethine), by heating codeine methiodide with alkali.

Six isomeric methylmorphimethines are known. In α-methylmorphimethine, the alcoholic hydroxyl and the double bond in the hydroaromatic ring are believed to occupy the same positions as in codeine. By the action of alcoholic potash (6) or heat (7), the double bond is shifted, and β-methylmorphimethine is formed. γ-Methylmorphimethine, derived from isocodeine (8), is a stereoisomer of α-methylmorphimethine, differing from it only in the relative positions of hydrogen and hydroxyl on C-6. It suffers a similar rearrangement of the double bond, giving δ-methylmorphimethine (9). The β- and δ- forms are therefore stereoisomers, and are structural isomers of the stereoisomeric pair, α- and γ-. ϵ-Methylmorphimethine, from pseudocodeine (10), has the alcoholic hydroxyl group on C-8, and ζ-methylmorphimethine, from allopseudocodeine (11) is its stereoisomer in which the H– and OH– on C-8 occupy the reverse positions.

In the earlier formulas for α- and γ-methylmorphimethine the double bond in ring III was assigned the 8, 14-position; in the rearrangement it was assumed to move to the 14, 13-position (12).



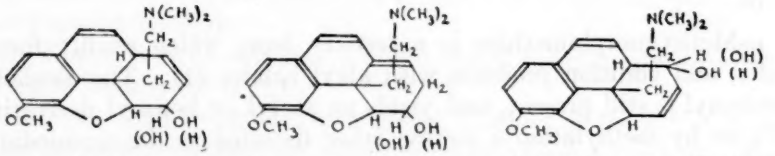
α-Methylmorphimethine (1907)



β-Methylmorphimethine (1907)

This represents the β- and δ-isomers as naphthalene derivatives, whence they should hydrogenate with much more difficulty than the α- and γ-derivatives. This is however not the case (13).

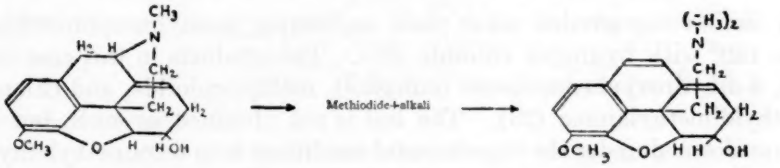
The ε- and ζ-isomers do not undergo a rearrangement in the sense of the α- to β- change, presumably because the double bond already occupies the most stable position, and the driving force given by the possibility of forming a conjugated system is lacking.



α- and γ-Methylmorphimethines ε- and ζ-Methylmorphimethines
β- and δ-Methylmorphimethines

As would be expected from this conception, α- and β-methylmorphimethine yield the same tetrahydro derivative. Hydrogenation of the γ- and δ-isomers similarly results in one tetrahydro compound, different from that obtained from the α- β-isomers (i. e. stereoisomeric) (13). (*Cf.* Faltis (14).)

Further confirmation of this rearrangement of the double bond has recently been found in the degradation of neopine. This naturally occurring alkaloid is a fifth codeine, differing from ordinary codeine only in the position of the double bond in ring III. (See Neopine, p. 205.) It degrades directly to β-methylmorphimethine (15).



Neopine β-Methylmorphimethine

The chemistry of the isomeric methylmorphimethines will be considered in detail in the following paragraphs. For convenient reference the properties of these compounds are tabulated below:

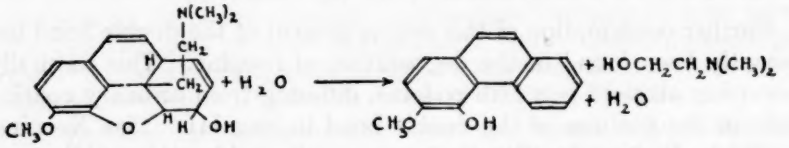
The isomeric methylmorphimethines

Isomer	m. p.	$[\alpha]_D$	Methiodide		Benzoate		Hydrochloride		Methyl ether		Corresp. codeine
			m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	
	°	°	°	°	°	°	°	°	°	°	
α	118–119	−212	245	−112	138	−112.8	[1] 105		94	−251.9	Codeine.
β	134–135	+438	300–303	+247	157	+254			82	+432	Neopine.
γ	166–167	+64.6	265	+34.7	99–103	+41.3			41		Isocodeine.
δ	111–113	{+256.6 +284}	282–284	+150.7	98–108	+181			71–72		
ε	130	−120	198	−112			[1] 150	{−149 −154}	75	−92.8	Pseudocodeine.
ζ	([2])	−178	ca. 180	−148							Allopseudocodeine.

[1] Decomposition.
[2] Oil.

α-Methylmorphimethine is a tertiary base, which readily forms salts, and addition products with alkyl halides (1). The alcoholic hydroxyl is still present, and yields an acetyl or benzoyl derivative (1), or by methylation a methyl ether (isolated as the methiodide) (16) (17).

When α-methylmorphimethine is heated with acetic anhydride (18) (19) (20) it breaks down into a phenanthrene derivative, methylmorphol (21) (see p. 281), ethanoldimethylamine (20) (22), and, to some extent, into dimethylamine (19) as follows (21):

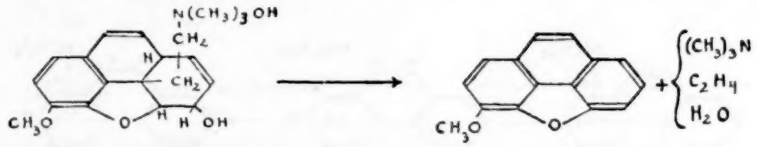


α-Methylmorphimethine Methylmorphol

A similar degradation takes place on heating methylmorphimethine to 180° with hydrogen chloride (22). The products in this case are 3, 4-dihydroxyphenanthrene (morphol), methyl chloride, and chloroethyldimethylamine (23). The last is not obtained as such, but is transformed under the experimental conditions into tetramethylethylenediamine and ethanoldimethylamine (24). The action both of acetic anhydride and of hydrochloric acid results in conversion of a portion of the α-methylmorphimethine into the β-isomer, which is regained from the reaction, as it is stable toward the reagents employed. The action of sodium ethylate on either α- or β-methylmorphimethine leads also to methylmorphenol; in this case the basic fraction is dimethylaminoethyl ethyl ether (23).

The methylmorphimethines may be converted to phenanthrene derivatives by gentler processes; α-methylmorphimethine methiodide,

with silver oxide or alkalies, goes to the quaternary base, which on heating decomposes as follows (19) (25):

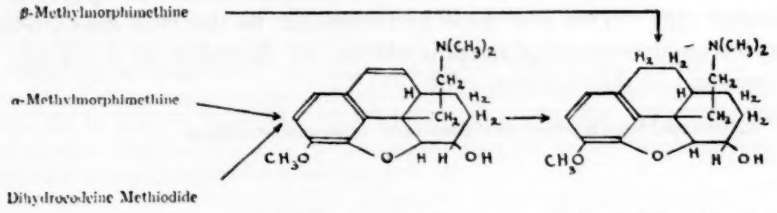


α-Methylmorphimethine Methohydroxide Methylmorphenol

The Hofmann degradation takes here an unexpected course, inasmuch as only the loss of trimethylamine and water with establishment of a new double bond would be expected. The tendency of the system to become completely aromatic is sufficiently great to cause extrusion of the entire side chain. (*Cf.* Robinson (26).) In the case of certain tetrahydro derivatives (13) the degradation takes a more normal course (see chloro-α-methylmorphimethine, and tetrahydro-γ-methylmorphimethine, below).

By distillation with zinc dust, α-methylmorphimethine gives phenanthrene in small yield (22).

Catalytic hydrogenation (with nickel, method of Rupe)[97] reduces α-methylmorphimethine to dihydro-α-methylmorphimethine (von Braun (31)) identical with the des-N-methyldihydrocodeine resulting from the degradation of dihydrocodeine (27) (28). The unsaturation in the 7, 8-position is first satisfied. Further reduction saturates the 9, 10-double linkage, giving tetrahydro-α-methylmorphimethine (the dihydro-des-N-methyldihydrocodeine of Freund). This same tetrahydro compound is obtained by catalytic reduction of β-methylmorphimethine (13), showing that the isomerism of the α- and β-methylmorphimethines depends upon the unsaturated linkages.*

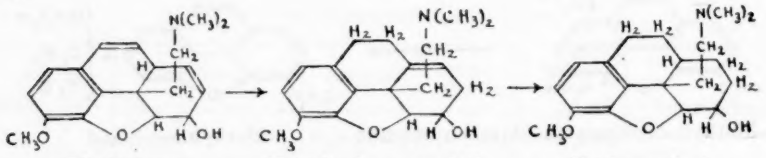


Dihydro-α-methylmorphimethine Tetrahydro-α-methylmorphimethine

Reduction of α-methylmorphimethine with sodium and alcohol gives a hydromethylmorphimethine (29) different from that of Freund and Wieland. In it the 9, 10-double linkage has been saturated (27); its stability suggests further that it belongs to the β-series (29) (*cf.* ref. 30), which finds confirmation in its preparation from β-methyl-

* See Appendix, p. 365.
[97] Helv. Chim. Acta **2**, 205 (1919).

morphimethine (V. Braun (31)). It is converted into the above-mentioned tetrahydro-α-methylmorphimethine by catalytic hydrogen (27).



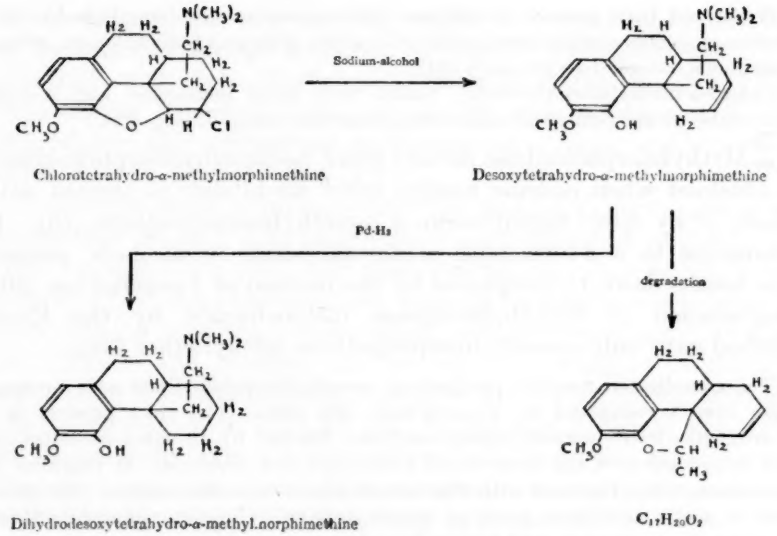
α-Methylmorphimethine — Tetrahydro-α-methylmorphimethine — Hydromethyl morphimethine

Degradation of tetrahydro-α-methylmorphimethine was unsuccessful (27) (28). From dihydro-α-methylmorphimethine (Δ-9,10), however, Speyer and Krauss (32) obtained a crystalline, nitrogen-free product, $C_{17}H_{18}O_3$. This was found to be isomeric with the end-product from degradation of dihydroisocodeine; the hydroxyl groups to which the isomerism of codeine and isocodeine is due evidently retain their respective configurations throughout the changes involved.

Tetrahydro-α-methylmorphimethine can be oxidized with chromic acid to the corresponding ketone (50), dihydro-des-N-methyldihydrocodeinone, whose preparation by other methods is described in the chapter on codeinone (p. 252).

Tetrahydro-α-methylmorphimethine yields with phosphorous pentachloride chlorotetrahydro-α-methylmorphimethine (13), apparently identical with that obtained by reduction of the methine base from chlorodihydrocodide (28) (p. 215). Chlorotetrahydro-α-methylmorphimethine is very stable toward hydrolysis, but reduces with sodium in alcohol to desoxytetrahydro-α-methylmorphimethine (33), the dihydrodesoxytetrahydro-α-methylmorphimethine of Speyer and Koulen (13). This new base hydrogenates to the true dihydrodesoxytetrahydro-α-methylmorphimethine, or degrades to $C_{15}H_{16}O_2$, a compound of the thebenol type (33).[98]

[98] The structural formula printed for this substance corresponds to $C_{17}H_{20}O_2$.



Chlorotetrahydro-α-methylmorphimethine

Desoxytetrahydro-α-methylmorphimethine

Dihydrodesoxytetrahydro-α-methylmorphimethine

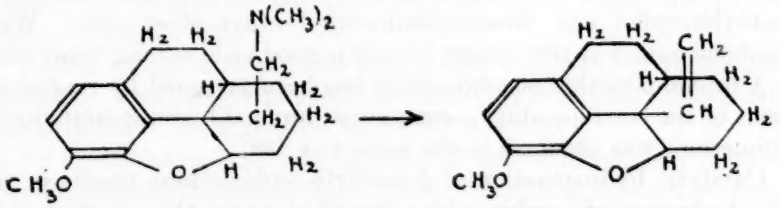
$C_{17}H_{20}O_2$

Tetrahydro-α-methylmorphimethine forms an amine oxide, from which two isomeric N-oxide sulphonic acids are derived (13); the nature of the isomerism is not known. The amine oxide of α-methylmorphimethine gives but one sulphonic acid.

Chloro-α-methylmorphimethine results from the action of phosphorous trichloride (34) or better, phosphorous pentachloride (35) on α-methylmorphimethine. In analogy with the behavior of chlorocodide, it hydrolyzes to give γ-, δ-, and ε-methylmorphimethines (36), and, conversely, it is obtained when γ-methylmorphimethine is treated with phosphorous pentachloride (13). A dichloromethylmorphimethine is also known (34).

The degradation of chloro-α-methylmorphimethine yields methylmorphol, ethanoldimethylamine, and chloroethyldimethylamine (isolated as dimethylpiperazine), according to the conditions (34) (36).

Catalytic hydrogenation of chloro-α-methylmorphimethine results in the formation of isomeric desoxy-methine bases, $C_{19}H_{27}O_2N$; one of these isomers degrades to a vinyl derivative, $C_{17}H_{20}O_2$ (compare with the loss of the entire ethanamine chain in the case of the unhydrogenated methylmorphimethines), while the other proves to be very resistant (13):



Desoxy-methine Bases

Nitrogen-free Product

It has not been possible to prepare chloro-α-methylmorphimethine by ring scission of α-chlorocodide methiodide (37); alkali splits out both halogens, giving amorphous halogen-free products (34).

Chloro-α-methylmorphimethine, boiled with ethyl mercaptan and sodium alcoholate, yields β-ethylthiomethylmorphimethine (55). (See p. 234.)

α-Methylmorphimethine methyl ether (α-dimethylmorphimethine) is obtained when codeine methyl ether methiodide is treated with alkali, or by direct methylation of α-methylmorphimethine (16). It rearranges to a β-form with acetic anhydride or alcoholic potash; this breaks down to morphenol by the method of Vongerichten (30). Degradation of dimethylmorphine methochloride by the Emde method gave only α-methylmorphimethine methyl ether (38).

The complicated reaction products of α-methylmorphimethine with bromine have been investigated by Vongerichten (39) (40). The chief product is a hydroxydihydrobromomethylmorphimethine, formed by bromine substitution, and introduction of the elements of water into the molecule. It degrades to a bromomorphol, identical with that obtainable from bromocodeine. Bromination in acetic anhydride gives an acetoxybromodihydromethylmorphimethine, in which the bromine is very loosely bound.

The action of cyanogen bromide on acetyl-α-methylmorphimethine has been studied by von Braun (41).

Oxymethylmorphimethine (ketodihydromethylmorphimethine), which results from degradation of hydroxycodeine, is treated in the section devoted to that base.

β-METHYLMORPHIMETHINE

This base is formed by a rearrangement of the 7, 8-double linkage of α-methylmorphimethine into the 8, 14-position. The change may be brought about by heat (7) or heat and chemical agents, as hydrogen chloride (22), acetic anhydride, water, 50% alcohol, or best by alcoholic potash (6). β-Methylmorphimethine results directly from the ring scission of neopine methiodide (15).

Hesse (1) first observed the isomer as the methiodide. It was rediscovered later by Knorr (19) (20) (22) who believed it at first to be a stereoisomer, then recognized the nature of the isomerism (12). The recent evidence for this has been discussed in the introduction to this section.

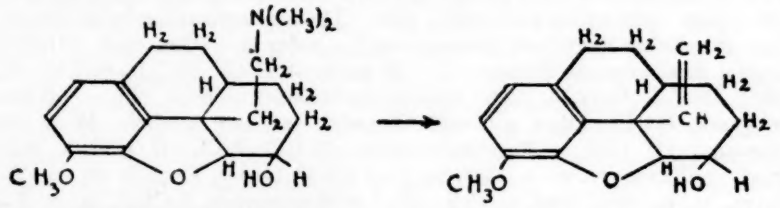
β-Methylmorphimethine is much more stable than the α-modification, and is often found among the degradation products from the latter. By vigorous action of sodium ethylate it breaks down into methylmorphol and dimethylaminoethyl ethyl ether (23). With alcoholic potash at 160° it may be split in good yield to morphenol (30).

A bromo-β-methylmorphimethine has been prepared by rearrangement of the corresponding α-compound; bromodihydro-β-methylmorphimethine was obtained in the same way (39).

Catalytic hydrogenation of β-methylmorphimethine results in the tetrahydromethylmorphimethine described under the α-isomer (13). When nickel (Rupe's method) is used as the catalyst, β-methylmorphimethine takes up one molecule of hydrogen, saturating the 9, 10-

double linkage; the same dihydro-β-methylmorphimethine is obtained by sodium and alcohol reduction of β-methylmorphimethine. It is identical with the dihydromethylmorphimethine resulting from reduction of α-methylmorphimethine (29) with sodium and alcohol; it is evident that a structural rearrangement of the α- into the β-form takes place in this reduction (31).

γ-Methylmorphimethine is formed by ring scission from isocodeine methiodide (8) (42), or by hydrolysis of α-chloromethylmorphimethine (36). It regenerates the latter when treated with phosphorous pentachloride (13). Like the α-isomer, γ-methylmorphimethine rearranges under the influence of alcoholic potash, giving δ-methylmorphimethine (9). The γ- and δ-isomers are converted by catalytic hydrogen to one tetrahydro-γ-methylmorphimethine, which may be degraded into the N-free compound $C_{17}H_{20}O_3$ (13); in this case, exhaustive methylation apparently takes a normal course, with formation of a nitrogen-free vinyl compound as would be expected from the Robinson theory in a case where ring III is completely hydrogenated.



Tetrahydro-γ-methylmorphimethine

γ-Methylmorphimethine methyl ether has been prepared by direct methylation, as well as from isocodeine methyl ether (16) (43).

ϵ-Methylmorphimethine is derived from pseudocodeine methohydroxide (10) (42) (44); it is likewise obtained when α-chloromethylmorphimethine is hydrolyzed (36). Unlike the α- and γ-isomers, it cannot be isomerized. Under the influence of acetic anhydride, or by the Hofmann method, it breaks down into the same end-products as does the α-isomer (36) (44). With catalytic hydrogen ϵ-methylmorphimethine yields a hexahydro derivative, by saturation of the two multiple linkages and opening of the ether ring. The (acetyl) hexahydro compound, has been degraded to a thebenol-type substance, $C_{19}H_{24}O_4$ (13).

Pseudocodeine methyl ether methiodide with alkali gives the corresponding ϵ-methylmorphimethine methyl ether, also known from methylation of the ϵ-methine base (16) (43).

By methylation and ring opening of allopseudocodeine the sixth isomer, ζ-methylmorphimethine was obtained; this does not rearrange (11). On hydrogenation, a hexahydro-ζ-methylmorphimethine is formed, different from the hexahydro derivative of the ϵ-isomer (13).

β-Morphimethine is the only known representative of the morphimethines containing the free phenolic hydroxyl. It was obtained by Vongerichten (45), from the action of acetic anhydride on morphine methohydroxide. Apparently the first stage of the morphol scission is the formation of an α-morphimethine; this breaks down for the most part into diacetylmorphol, but a small portion rearranges to the more stable β-isomer before degradation takes place (45). β-morphimethine is converted to β-methylmorphimethine methiodide by methyl iodide in the presence of sodium methylate (45).

The ethylthiomethylmorphimethines are discussed on page 234.

Descriptive Part (Methylmorphimethines)

α-METHYLMORPHIMETHINE: B = $C_{19}H_{23}O_3N$. Prep. from 303 g. morphine (hydrated cryst.) in 1 liter CH_3OH containing 24 g. dissolved sodium. This is refluxed two hours with 350 g. CH_3I, and the codeine methiodide which crystallizes out (400 g.) separated and washed with alcohol. It is dissolved in 2 liters of boiling water, and boiled 10 minutes with 500 c. c. of 25% sodium hydroxide. The dark oil which forms is washed with water and crystallized by pouring into ether, or by dissolving in three times its vol. of alcohol and precipitating cautiously with water. 230–240 g. yield (80%) (22). The base crystallizes from alcohol or ether in colorless anhydrous prisms, from hot water in needles, cont. 1 H_2O (1). Crystal measurements, Pschorr. (7). It melts at 118.5° (1) (3), $[\alpha]_D^{17} = -212°$ (99% alcohol, C = 2.13) (22); cryoscopic behavior normal (46). —HYDROCHLORIDE, B·HCl + $2H_2O$, sol. 1:11 in water, very sol. alcohol. M. p. 105° (decomp.) (1) (22). —PLATINICHLORIDE, $(B \cdot HCl)_2PtCl_4 + H_2O$, dark yellow cryst. —BENZOATE, m. p. 138°, $[\alpha]_D^{16} = -112.8°$ (water, C = 1.0) (9). —TARTRATE, m. p. 165°, insol. alcohol (22). —METHIODIDE, B·CH_3I, m. p. 245°, $[\alpha]_D = -112°$ (99% alcohol) (11), $[\alpha]_D^{17} = -94.56°$ (99% alcohol, C = 1.4) (22). —METHOCHLORIDE, and its Platinichloride (1). ACETYL-α-METHYLMORPHIMETHINE, cryst. from water, m. p. 66°, $[\alpha]_D^{17} = -96.3°$ (99% alcohol, C = 2.698); it gives a cryst. Hydrochloride (+ ½H_2O), Platinichloride, Nitrate, and Sulphate. The Methiodide m. 207°, $[\alpha]_D^{17} = -73.8°$ (99% alcohol, C = 0.568) (1) (22) (47); Methobromide, m. p. 207° to 208° (41). BENZOYL-α-METHYLMORPHIMETHINE, needles of m. p. 182° to 183°, giving a Methiodide, m. p. 188° (34). —CARBANILIDE, from the action of phenylisocyanate, needles of m. p. 122° to 123°, whose Methiodide m. 251° (22). —METHYL ETHER (α-dimethylmorphimethine), cryst. from CH_3OH, needles of m. p. 94°, $[\alpha]_D^{24} = -251.9°$ (methanol, C = 2.085); gives a Methiodide m. p. 256° (263°), $[\alpha]_D^{23} = -134.4°$ (water, C = 0.260) (16) (17) (38). —N-OXIDE, prisms from water, decomp. 188° (13).

PIPERIDO-α-METHYLMORPHIMETHINE: from piperidocodide methiodide; oil, giving a Platinichloride, and a Monomethiodide, m. p. 248°, Dimethiodide not crystalline (48).

NITRO-α-METHYLMORPHIMETHINE, see Nitrocodeine (p. 193).

CHLORO-α-METHYLMORPHIMETHINE: $C_{19}H_{22}O_2NCl$, from base with PCl_3 (34), α- or γ-base with PCl_5 (13) (36). Free base oily, Hydrochloride, m. 177° to 178°; Methiodide, m. p. 163° (167°). Hydrolysis of base, Pschorr (36), rearrangement by heat (35); reduction, Speyer (13).

DICHLORO-α-METHYLMORPHIMETHINE: $C_{19}H_{23}O_3NCl_2$, from action PCl_5; needles from alcohol, m. p. 180° to 181°; Methiodide, m. p. 153° to 154° (34).

BROMO-α-METHYLMORPHIMETHINE (37) (39): $C_{19}H_{22}O_3NBr$, from bromocodeine methiodide (Br in aromatic nucleus). M. p. 132°, melting again at 182° to 184° (probably the β-form); $[\alpha]_D^{15} = -104.06°$ (99% alcohol, C = 1.2252);

Methiodide, crystalline; $[\alpha]_D^{15} = -110.71°$ (C=0.56) (39) (40); Platinichloride ($+4H_2O$), yellow crystals. Acetyl derivative isolated as platinum salt ($+2H_2O$), forms also a cryst. Hydrobromide, decomp. 235°, and Hydriodide, decomp. 222°. ACETYLDIBROMODIHYDRO-α-METHYLMORPHIMETHINE HYDROBROMIDE, from acetyl-α-methylmorphimethine with Br_2 in dil. acetic acid, cryst. decomp. at 202°, $C_{21}H_{25}O_4NBr_2 \cdot HBr$.

BROMOHYDROXYDIHYDRO-α-METHYLMORPHIMETHINE (39) (40): $C_{19}H_{24}O_4NBr$, from α-methylmorphimethine with Br_2 in $CHCl_3$, cryst. from methanol, m. p. 170°; cryst. Methiodide, decomp. ca. 150°, which degrades to bromomorphol; Acetyl deriv. ($+C_6H_6$), decomp. 118° to 138°. The Methyl ether m. 112° and gives an Acetyl deriv., m. p. 126°, $[\alpha]_D^{26} = +108.4°$ (methanol, C=2.468) (49).

DIHYDRO-α-METHYLMORPHIMETHINE: (des-N-methyldihydrocodeine), B=$C_{19}H_{25}O_3N$. From degradation of dihydrocodeine methiodide (27) (28), or hydrogenation of α-methylmorphimethine (31);[99] oily, isolated as —HYDROCHLORIDE, m. p. 133°. —PERCHLORATE, m. p. 201° to 202°. —METHIODIDE, B·$CH_3I + H_2O$, m. p. 160° (27) (31), 173° (28), anhydrous, m. p. 223° to 225°; it degrades to $C_{17}H_{18}O_3$, m. p. 115°.

BROMODIHYDRO-α-METHYLMORPHIMETHINE (39): $C_{19}H_{24}O_3NBr$, from dihydro-α-methylmorphimethine with bromine; m. p. 165°; Methiodide, m. p. 264°.

TETRAHYDRO-α-METHYLMORPHIMETHINE: (13) (27) (28) (50), B=$C_{19}H_{27}O_3N$, oil, distilling at 230° to 240° /15 mm. (partial decomp.). —HYDROCHLORIDE, B·HCl+$2H_2O$, m. p. 94°; anhydrous, m. p. 228°; $[\alpha]_D^{18} = -31.9°$ (water, C=0.974). —HYDRIODIDE, B·HI, decomp. 251°. —PERCHLORATE, m. p. 218° to 219°. —NITRATE, m. p. 174° to 175°. —PLATINICHLORIDE, m. p. 202°. —METHIODIDE, m. p. 220° to 221°. ACETYLTETRAHYDRO-α-METHYLMORPHIMETHINE (13), oily, but forms Hydriodide, m. p. 223°, and Hydrobromide, m. p. 230°; Methobromide, m. p. 225° to 226° (31). NITROTETRAHYDRO-α-METHYLMORPHIMETHINE, isolated as Nitrate, m. p. 220° to 221°. CHLOROTETRAHYDRO-α-METHYLMORPHIMETHINE (13), base, oily, giving a Methiodide, m. p. 286° (decomp.), a Hydrochloride, m. p. 267° (decomp.) and a Hydrobromide of m. p. 236°. —METHYL ETHER: (α-tetrahydrodimethylmorphimethine), from cat. red. of α- or β-methylmorphimethine methyl ether (14). Crystals of m. p. 43° to 46°, giving an Aurichloride, decomp. 143°, and a Methiodide, decomp. 247°, $[\alpha]_D^{20} = -40°$ (dil. alcohol). —N-OXIDE: $C_{19}H_{27}O_4N + 1\frac{1}{2}H_2O$, m. p. 94°. Forms a sulphonic acid, occurring in two modifications, decomp. 295° and 270° resp. (13).

DESOXYTETRAHYDRO-α-METHYLMORPHIMETHINE (33): $C_{19}H_{27}O_2N$ (Speyer's dihydrodesoxytetrahydro-α-methylmorphimethine) (13) from chlorotetrahydro-α-methylmorphimethine, reduced with Na in absol. alcohol. Cryst. from bromobenzene, m. p. 163° to 164°; Methiodide, m. p. 248°; Perchlorate, m. p. 159°; the Methyl ether gives a Methiodide, m. p. 210° to 212°, Hydriodide, m. p. 170° to 171°, Perchlorate, m. p. 206° to 208°.

DESOXYTETRAHYDRO-α-METHYLMORPHIMETHINE (Speyer) (13): $C_{19}H_{27}O_2N$, from cat. red. of chloro-α-methylmorphimethine with $3H_2$; cryst. from alcohol-water, m. p. 156°; Methiodide, 235°. An isomer from the same reaction is oily, gives a Hydrobromide, decomp. 215° to 220°, Hydriodide, m. p. 208° to 210°, Methiodide, decomp. 272° to 273°.

DIHYDRODESOXYTETRAHYDRO-α-METHYLMORPHIMETHINE (Cahn) (33): $C_{19}H_{29}O_2N$, cryst. from chlorobenzene, m. p. 152.5° to 154°; Hydriodide, m. p. 219° to 220°; Perchlorate, m. 150° to 153°; Methiodide, 230°. The Methyl ether is an oil, forms a Hydriodide, m. p. 174° to 176°, Perchlorate, m. p. 194° to 195°, Methiodide not cryst. This methyl ether also obt. by Zn-HCl red. of dihydromethyldihydrothebainonemethine.

[99] A dihydro-α-methylmorphimethine is mentioned by Vongerichten (39) (1907), with no description of its preparation or properties.

α-CYANONORMETHYLMORPHIMETHINE (31) (41) (47): $C_{19}H_{20}O_3N_2$, from BrCN on acetyl-α-methylmorphimethine, m. p. 109°, $[\alpha]_D^{19} = -196°$; Acetyl compound, m. p. 108°, $[\alpha]_D^{16} = -106°$ (alcohol).

TETRAHYDROCYANONORMETHYLMORPHIMETHINE (31): $C_{19}H_{24}O_3N_2$, plates from methanol, m. p. 140°, $[\alpha]_D^{20} = -51.4°$ ($CHCl_3$). The Acetyl derivative m. 100° to 101°. Tetrahydronormethylmorphimethine (31) is an oil, yielding a Chloro derivative whose Hydrochloride $C_{18}H_{24}O_2NCl \cdot HCl$ m. 267° (decomp.), and Platinichloride decomp. 223°.

METHYLMORPHIMETHYL-MORPHOLINE (51): Prep. by ring scission of norcodeinium-morpholinium iodide. Base oily, giving Acetyl derivative, m. p. 118° to 120°, whose Platinichloride m. 177°.

METHYLMORPHIMETHYL-DIHYDROISOINDOL (51): $C_{25}H_{23}O_3N$, m. p. 110°, Acetyl deriv. m. p. 146° whose Hydrochloride m. 224° and Methiodide m. 163°.

METHYLMORPHIMETHYL-PIPERIDINE (51): $C_{22}H_{27}O_3N$, m. p. 93° to 94°, Platinichloride, m. p. 174°, Acetyl deriv. m. p. 87°.

β-MORPHIMETHINE (45): $B = C_{18}H_{21}O_3N$, from action acetic anhydride on morphine methohydroxide, isolated as the Hydrochloride, $B \cdot HCl + H_2O$, white needles.

β-METHYLMORPHIMETHINE: $B = C_{19}H_{23}O_3N$, prep. by refluxing 20 g. α-methylmorphimethine with 20 g. KOH in 200 c. c. 60% alcohol for two hours. The oil obt. after distilling off alcohol solidifies, yield 19–20 g., recryst. from alcohol; colorless prisms, m. p. 134° to 135°; $[\alpha]_D^{17} = +438°$ (97% alcohol, C=1.0) (6). For prep. *cf.* also Pschorr (7). A large number of salts were analyzed by Hesse (1). —BENZOATE, cryst. from alcohol, m. p. 157°, $[\alpha]_D^{17} = +254°$ (water, C=1.0) (6) (7). —METHIODIDE (6) (7) (15), m. p. 300° to 303° (291°) (decomp.), $[\alpha]_D^{19} = +247°$ (90% alcohol, C=0.352), $[\alpha]_D^{17} = +233°$ (97% alcohol, C=0.6). (Neopinemethine methiodide), $[\alpha]_D^{21} = +262°$, (90% alcohol, C=0.3), $[\alpha]_D^{21} = +241.1°$ (methanol, C=0.506). FORMYL-β-METHYLMORPHIMETHINE (52), isolated as the Hydrochloride. ACETYL-β-METHYLMORPHIMETHINE, noncrystalline, $[\alpha]_D^{17} = +413.9°$, (99% alcohol, C=0.798); Methiodide, amorphous, $[\alpha]_D^{17} = +257.6°$ (99% alcohol, C=0.59) (22). —METHYL ETHER: (β-dimethylmorphimethine) (16) (17) (43), $C_{20}H_{25}O_3N$, cryst. from pet. ether, m. p. 82°, $[\alpha]_D^{17} = +432°$ (absol. alcohol, C=0.757). The Hydriodide decomp. 243°, the Methiodide, m. p. 318° to 320° (corr.) (320° to 330°), $[\alpha]_D^{22} = +268.5°$ (+278.5°) (water, C=0.23).

DIHYDRO-β-METHYLMORPHIMETHINE, from α-methylmorphimethine with sodium and alcohol (29) (30), or from the β-isomer by catalytic red (31). Base is oily, but gives Methiodide, m. p. 263°, and an Acetyl cpd. whose Methiodide m. 265° and shows $[\alpha]_D^{22} = +76°$.

ACETO-β-METHYLMORPHIMETHINE (53): $C_{21}H_{25}O_4N$, from acetocodeine methiodide, needles, m. p. 149°, $[\alpha]_D^{21} = +150°$ ($CHCl_3$, C=5.6635). It gives an Acetyl deriv. whose Methiodide m. 180° to 182°.

BROMO-β-METHYLMORPHIMETHINE (39): $C_{19}H_{22}O_3NBr$, from degradation of bromomorphine, m. p. 184°, $[\alpha]_D^{15} = +128.22°$ (99% alcohol, C=0.7128); Methiodide not cryst.

BROMODIHYDRO-β-METHYLMORPHIMETHINE (39): $C_{19}H_{24}O_3NBr$, from the action of Br_2 in $CHCl_3$ on dihydro-β-methylmorphimethine; m. p. 169°; gives a Methiodide, m. p. 277°.

NOR-β-METHYLMORPHIMETHINE UREA (31): $C_{19}H_{22}O_4N_2$, prep. by hydrolysis of the oily cyanonor-β-methylmorphimethine; m. p. 130° to 131°, $[\alpha]_D^{18} = +364°$ ($CHCl_3$).

γ-METHYLMORPHIMETHINE: $B = C_{19}H_{23}O_3N$. Prep. by boiling for 12 minutes 5 g. of isocodeine methiodide in 25 c. c. of water with 6 c. c. of 25% NaOH solution. An oil separates when the solution is cooled, and soon solidifies. It is recryst.

from alcohol, yielding tablets, m. p. 167°, (169°), $[\alpha]_D^{20} = +64.6°$ ($CHCl_3$, C= 3.094) (8). —HYDROCHLORIDE, crystalline, —BENZOATE, m. p. 100° (9), $[\alpha]_D^{15} = +41.3°$ (99% alcohol, C=0.8685). —HYDRIODIDE, m. p. 238° to 239°, $[\alpha]_D^{20} = +37°$ (water, C=0.811) (36). —METHIODIDE, m. p. 265° (cryst. from alcohol), $[\alpha]_D^{17} = +34.7°$ (water, C=1.56)(8). —METHYL ETHER; (γ-dimethylmorphimethine) (43) B=$C_{20}H_{25}O_3N$ from isocodeine methyl ether methiodide, m. p. 41°; Hydriodide, B·HI+H_2O, m. p. 192° to 193°, $[\alpha]_D^{22} = +20.31°$, (water, C=0.64); Methiodide, m. p. 259° (decomp.), $[\alpha]_D^{20} = +14°$ (water) (16) (17).

TETRAHYDRO-γ-METHYLMORPHIMETHINE (13): B=$C_{19}H_{27}O_3N$, prep. by catalytic reduction. Cryst. from dil. alcohol in octahedra, m. p. 115°, $[\alpha]_D^{18} = -29.2°$ (dil. acetic acid); Hydrochloride, B·HCl+$3H_2O$, decomp. 273°; Hydriodide, B·HI, decomp. 265°; Sulphate, crystalline; Methiodide, decomp. ca. 300°; Acetyl deriv., m. p. 90° to 91°, gives a Hydriodide, m. 220°, and Methobromide (+$3H_2O$), m. p. 100° to 102° (31).

TETRAHYDROCYANONOR-γ-METHYLMORPHIMETHINE (31): M. p. 117°, $[\alpha]_D^{17} = -90.7°$ ($CHCl_3$); Acetyl deriv., m. p. 102°, $[\alpha]_D^{16} = -104.5°$ ($CHCl_3$).

δ-METHYLMORPHIMETHINE: B=$C_{19}H_{23}O_3N$. Prep. by refluxing for several hours 6 parts of γ-methylmorphimethine in 36 parts of alcohol with 30 parts 20% aqueous KOH. The oil left by distilling off alcohol was dissolved in ether, from which it crystallized on concentration. Recryst. from ether, m. p. 111° to 113°, $[\alpha]_D^{15} = +256.6°$ (absol. methanol). Very sol. in methyl or ethyl alcohol, benzol, acetone or ethyl acetate (9). Reduction, Speyer (13). —BENZOATE, cryst. from water, m. p. 99° to 108°, $[\alpha]_D^{15} = +181.1°$ (99% alcohol, C=0.6315). —METHIODIDE, cryst. from water, m. p. 282° to 284°, $[\alpha]_D^{15} = +150.7°$ (absol. alcohol C=1.003) (9); $[\alpha]_D^{15} = +158.7°$ (methanol, C=0.655(36)). —METHYL ETHER (43): Cryst. from 50% methanol, leaflets, m. p. 71° to 72°, giving a Hydriodide of m. p. 212°, and Methiodide, m. p. 286°, $[\alpha]_D^{28} = +170.9°$ (water, C=0.439) (16).

ε-METHYLMORPHIMETHINE: B=$C_{19}H_{23}O_3N$, prep. by adding 25 c. c. boiling 25% NaOH solution to a boiling solution of 10 g. of pseudocodeine methiodide in 100 c. c. water. After boiling a few minutes an oil sepd., cooled, and dissolved in ether. From the ether dried over K_2CO_3, a viscous oil, which crystallized. Recryst. from ether or a mixture of alcohol and hexane, m. p. 129° to 130°, $[\alpha]_D^{15} = -120.1°$ (99% alcohol, C=2.877) (44). *Cf.* Oppé (42). —HYDROCHLORIDE: B·HCl+H_2O, m. p. 150°, $[\alpha]_D^{15} = -154°$ (water, C=4.757) (10) (44). —HYDRIODIDE: B·HI, m. p. 210° to 213°, $[\alpha]_D^{20} = -95.6°$ (water, C=0.805) (36). —METHIODIDE: B·CH_3I, m. p. 196° to 198° (decomp.), $[\alpha]_D^{15} = -111°$ (water, C=1.255) (10) (11) (36) (44). ACETYL-ε-METHYLMORPHIMETHINE, not crystalline, gives a Methiodide, m. p. 205° to 210°, $[\alpha]_D^{15} = -45°$ (water, C= 0.491) (10) (36) (44). —METHYL ETHER, m. p. 75°, $[\alpha]_D^{18} = -92.84°$ (absol. alcohol, C=0.94), gives a Hydriodide, m. p. 207°, $[\alpha]_D^{15} = -85.5°$ (C=1.4035); Methiodide, m. p. 277°, $[\alpha]_D^{20} = -79.4°$ (methanol, C=0.283) (17) (36) (16) (54). BROMOHYDROXYDIHYDRO-ε-METHYLMORPHIMETHINE METHYL ETHER, from action Br_2 in $CHCl_3$, $C_{20}H_{26}O_4NBr$, m. 127° to 128° and gives a Hydriodide, m. 155° to 156° (49). —HYDRATES (36): Dihydrate, B+$2H_2O$, needles m. about, 100°, sol. water, insol. ether; Monohydrate, B+H_2O, decomp. about 112°, sol. water, insol. ether. It decomp. in vac. at 80° to give ε-methylmorphimethine. The monohydrate hydriodide, B·H_2O·HI, decomp. 226°, $[\alpha]_D^{18} = -82.40°$ (water, C=0.801); Methiodide, decomp. 253° to 254°. Monohydrate acetyl deriv., decomp. 130° to 131°, whose Hydriodide decomp. 170°. The monohydrate methyl ether melts at 102°, giving a Hydriodide, m. p. 135°.

HEXAHYDRO-ε-METHYLMORPHIMETHINE (13): $C_{19}H_{29}O_3N$, needles from ether, m. p. 155°. —HYDROCHLORIDE, plates, m. p. 213°. DIACETYLHEXAHYDRO-ε-

METHYLMORPHIMETHINE, an oil, giving a Methiodide, m. p. 255°. (*Cf.* Faltis (14).)

ζ-METHYLMORPHIMETHINE: B=$C_{19}H_{23}O_3N$, prep. by boiling allopseudocodeine methiodide with NaOH. Base is an oil, $[\alpha]_D^{15}=-178°$ (alcohol, C=10.955) (11). —METHIODIDE, powder melting about 180°, $[\alpha]_D^{15}=-148°$ (water, C=2.486).

HEXAHYDRO-ζ-METHYLMORPHIMETHINE (13): $C_{19}H_{29}O_3N$, by catalytic hydrogenation, cryst. from ethyl acetate, m. p. 174° to 175°, gives a Hydriodide decomp. 245°.

ETHYLTHIOMETHYLMORPHIMETHINES (55) are described on page 234.

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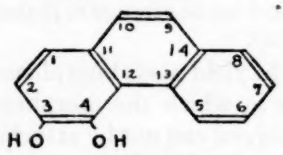
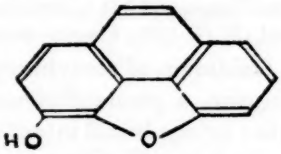
MORPHOL AND MORPHENOL

The degradation of the alkaloids of the morphine group to nitrogen-free products may be accomplished by two general methods. The action of acetic anhydride or hydrogen chloride on the bases or their quaternary addition compounds, yields derivatives of 3,4-dihydroxyphenanthrene, morphol. When the degradation is carried out by the exhaustive methylation method of Hofmann, derivatives of 3-hydroxy-4,5-phenanthrylene oxide, morphenol, are formed. The numerous



Morphol



Morphenol

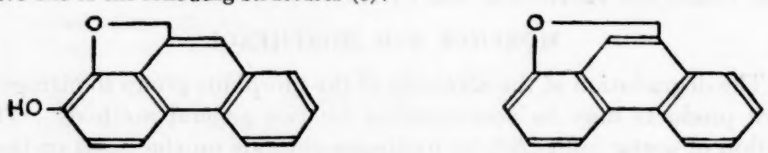
reactions which have led to morphol, morphenol, and other nitrogen-free phenanthrene derivatives, are arranged in tabular form at the end of this section. The evidence for the structure of morphol and morphenol, and its significance for the theory of morphine structure is discussed in the following paragraphs.

Diacetylmorphol is formed when morphine methiodide (1) or α-isomorphine methiodide (2) is heated with acetic anhydride. It may be saponified to morphol, which behaves as a typical diphenol, gives a strong ferric chloride test, and is oxidized with extraordinary ease (1). Diacetylmorphol can be oxidized to diacetylmorpholquinone, a substance of the phenanthrenequinone type (1), (3). It follows that neither of the hydroxyl groups of morphol is on the 9, 10-bridge carbon atoms. Morpholquinone, from hydrolysis of the diacetyl compound, oxidizes further to give phthalic acid (3), whence both hydroxyls must lie in the same aromatic nucleus (4), and are probably adjacent, since morpholquinone, in contrast to its monomethyl ether, is an excellent dye for mordanted fabrics. Analogy for this is to be found in the behavior of other ortho-dihydroxy compounds and their methyl ethers (3). The formation of protocatechuic acid in the alkali-fusion of morphine (5) may be regarded as confirming

the ortho-position of the two hydroxyl groups (4). Further evidence for the structure of morphol was obtained from a study of morphenol.

Morphenol (6), $C_{14}H_8O_2$, contains two less hydrogen atoms than morphol. One of the two oxygen atoms is present as a phenolic hydroxyl group (6); the second must be in an ether linkage, for on reduction of morphenol with sodium and alcohol it makes its appearance in the product, morphol, as a second phenolic hydroxyl (7). Morphenol yields phenanthrene on distillation with zinc dust (8) (9).

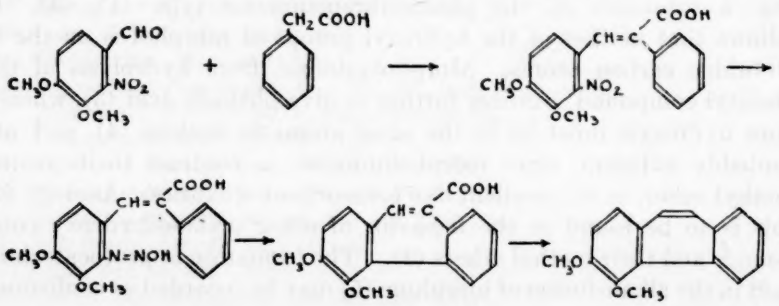
On the basis of the evidence given above, Vongerichten believed morphenol to have one of the following structures (3):



This hypothesis accounted for the reduction of morphenol to morphol derivatives, the conversion of morphenol to phenanthrene on distillation with zinc dust, a change which should not be possible with a 4, 5-phenanthrylene oxide, and likewise explained the oxidation of acetylmorphenol to a phenolic phenanthrenequinone derivative (10). These formulas were, however, without analogy in other series, and left unexplained the fact that morphol can be oxidized to phthalic acid (3) (4) (10), whereas morphenol can not (7) (11).

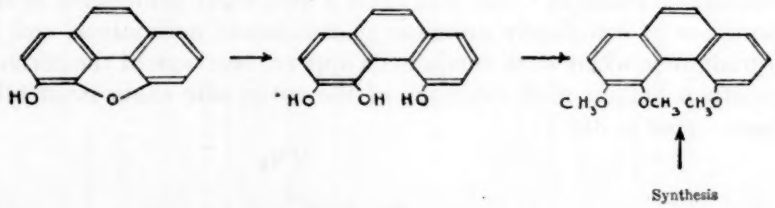
Oxidation of acetylmorphenol was found to yield acetylmorphenolquinone, a phenanthrenequinone derivative in which the morphenol ether bridge is still intact (11). The ether oxygen can not be attached to the 9- or 10-carbon atoms as originally postulated by Vongerichten, and must therefore link C-4 and C-5. The hydroxyl group formed on reductive scission of the ether ring must be attached to one of these carbon atoms; since the two hydroxyl groups are adjacent, morphol is considered to be 3, 4-dihydroxyphenanthrene, and morphenol to be 3-hydroxy-4, 5-phenanthrylene oxide (11).

The structure derived by Vongerichten for morphol was confirmed by Pschorr's synthesis of 3, 4-dimethoxyphenanthrene (12), which proved to be identical with morphol dimethyl ether (13). The synthesis was accomplished by condensation of o-nitrovanillin methyl ether with phenylacetic acid, followed by a Pschorr phenanthrene ring closure and decarboxylation:



Morphol itself, and morpholquinone, have been prepared from phenanthrene (14) (15) (16).*

In morphenol methyl ether, from the degradation of methylmorphine (codeine) the methoxyl group of codeine is still present, for the degradation of ethylmorphine yields morphenol ethyl ether (9). To obtain more direct proof of the location of the phenolic hydroxyl in morphine, Pschorr synthesized 3-hydroxy-4-methoxyphenanthrene, which proved to be different from methylmorphol (from degradation of codeine) (12). Methylmorphol must, therefore, be 3-methoxy-4-hydroxyphenanthrene. The last doubt of this was removed by the synthesis of 3-methoxy-4-acetoxyphenanthrenequinone (17), the acetylmethylmorpholquinone mentioned above, and by the splitting of the ether ring of morphenol with fused potassium hydroxide to yield a trihydroxyphenanthrene (18), whose trimethyl ether was identical with 3, 4, 5-trimethoxyphenanthrene synthesized by Pschorr (19).



Other degradations in the morphine series which lead to morphol derivatives will be briefly considered.

Thebaine, or its methiodide, degrades with acetic anhydride to acetylthebaol (20); when thebaine methiodide is heated with alkali (21) (22), or even with alcohol at 165° (22), the parent substance, thebaol is formed. Thebaol is 3-methyl-6-methoxymorphol, as was established by Freund (21), Vongerichten (23) and Pschorr (24) by methods similar to those outlined above. (See Thebaol, p. 294.)

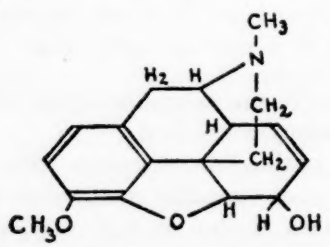
Codeinone breaks down on acetolysis to the acetyl derivative of 3-methoxy-4,6-dihydroxyphenanthrene (6-hydroxymethylmorphol) (25) which methylates to give the known (24) 3, 4, 6-trimethoxyphenanthrene (methylthebaol). Pseudocodeinone, on the other hand, is split by acetic anhydride to triacetylthebenine, whereas pseudocodeinone methiodide with alcohol at 170° yields 3-methoxy-4, 8-dihydroxyphenanthrene (26) (27), which methylates to give the synthetic (28) 3,4,8-trimethoxyphenanthrene. Codeinone and pseudocodeinone are direct oxidation products of codeine and pseudocodeine, respectively. By this degradation, the position of the alcoholic hydroxyl group in these isomeric codeines has been determined. 3,4,8-Trimethoxyphenanthrene has also been obtained from the

* See Appendix, p. 366.

degradation of apomorphine (29) (p. 261) and of methebenine (30) (p. 322).

The investigation of morphol and morphenol derivatives has shown beyond question that the functional groups in morphine are arranged on a phenanthrylene oxide skeleton, which must be partially hydrogenated. The morphine phenolic hydroxyl is located at C-3, the alcoholic hydroxyl at C-6 (degradation of codeinone). The 9, 10-bridge carbon atoms are hydrogenated, and to one of them the nitrogen of the ethanamine chain is attached (degradation of 9-hydroxycodeine, p. 179). Other facts of importance for the morphine structural theory are discussed in the section devoted to this (p. 336).

The extraordinary tendency of morphine and its derivatives to lose the entire ethanamine side chain on degradation has received a most plausible explanation in the structural theory recently advanced by Gulland and Robinson (31) (32). The novel feature of the Robinson formula consists in locating the carbon-to-carbon linkage of the ethanamine chain at C-13; this offers a structural hinderance to the formation of completely aromatic phenanthrene derivatives, and in degradations where such compounds appear, breakage of the carbon-to-carbon linkage with extrusion of the entire side chain must take place. (See p. 350.)



Codeine (Gulland and Robinson)

In those cases where the Hofmann degradation takes its normal course, with the formation of vinyl derivatives, the side chain is known to occupy a different position where it does not interfere with aromatization (e. g., thebenine, apomorphine, morphothebaine), or the bases are hydrogenated and aromatization is impossible (e. g., dihydrothebaine, tetrahydromethylmorphimethine). The presence of substituents in ring III prevents aromatization with loss of the side chain in the degradation of dihydrohydroxycodeinone to dihydrohydroxycodeone (33) (34), of dihydrohydroxythebainone to dihydrohydroxythebaone (34), of phenyldihydrothebaine to phenyldihydrothebenol (35), etc.

In the following tabular summary the more important degradations to phenanthrene derivatives are listed.

The more important degradations to phenanthrene derivatives

Compound	Method	Basic part	Nonbasic part
Morphine	Zinc dust distillation	Morphidine bases	Phenanthrene (10) (36) (37).
α-Methylmorphimethine	do		Phenanthrene (38).
Morphine methiodide	Acetic anhydride	Not investigated	Diacetylmorphol (1).
α-Isomorphine methiodide	do	do	Diacetylmorphol (2).
Codeine methiodide	do	do	Methylmorphol (1).
α-Methylmorphimethine	Dry HCl, 180°	Tetramethylethylenediamine and ethanoldimethylamine.	Morphol (38); Methylmorphol (38).
α-Methylmorphimethine α-Methylmorphiethine	Acetic anhydride	Ethanoldimethylamine	Acetylmethylmorphol (1) (39) (40).
β-Methylmorphimethine	Sodium ethylate	Dimethylaminoethyl ethyl ether	Methylmorphol (41).
ε-Methylmorphimethine	Acetic anhydride	Ethanoldimethylamine	Acetylmethylmorphol (42).
Chloromethylmorphimethine	do	Ethanolmethylamine and ethylanoldimethylamine.	Acetylmethylmorphol (43).
Do	Alcohol, 100°	N-dimethylpiperazine dimethochloride	Methylmorphol (44).
Dichloromethylmorphimethine	Acetic anhydride	Ethanolmethylamine and ethanoldimethylamine.	4-Acetyl-?-acetoxymethylmorphol (43).
Aceto-β-methylmorphimethine	Sodium ethylate	Dimethylaminoethyl ethyl ether	Acetomethylmorphol (45).
Bromomethylmorphimethine	Acetic anhydride	Not investigated	Bromomethylmorphol (46).
Hydroxydihydrobromomethylmorphimethine	do	do	Bromomethylmorphol (47).
Acetoxybromodihydromethylmorphimethine	do	do	3-Methoxy-4, 6-diacetoxyphenanthrene (47).
Acetoxybromodihydro-α-methylmorphimethine methyl ether.	do	do	Acetylthebaol (48).
Bromohydroxydihydro-ε-methylmorphimethine methyl ether.	do	do	3, 8-Dimethoxy-4-acetoxyphenanthrene (48).
Piperidomethylmorphimethine	do		Nonbasic compound, not acetylmethylmorphol (49).
Methyldesoxycodomethine	Spontaneous decomp	Not investigated	Dimethylmorphol (50).
Methyldesoxycodomethine methiodide	Alkali	Trimethylamine	Do.
Hydroxymethylmorphimethine	Acetic anhydride	Ethanoldimethylamine	Methoxydiacetoxyphenanthrene (51).
Codeinone	do	Ethanolmethylamine	3-Methoxy-4, 6-acetoxyphenanthrene (25).
Codeinone methiodide	Alcohol, 160°	Dimethylaminoethyl ethyl ether	6-Hydroxymethylmorphol (22).
Pseudocodeinone methiodide	do	do	8-Hydroxymethylmorphol (26).
Hydroxycodeinone	Hofmann degradation	Trimethylamine	Unstable (33).
Dihydrohydroxycodeinone	do	do	Dihydrohydroxycodeone (33).
Diacetylaminocodeine methiodide	Acetic anhydride	Not investigated	Triacetylaminomethylmorphol (52).
Thebaine Thebaine methiodide	do	Ethanolmethylamine	Acetylthebaol (20) (53).
Thebaine methiodide	Alcohol, 160°	Dimethylaminoethyl ethyl ether and dimethylamine.	Thebaol (22).
Thebaine	Benzoyl chloride	Ethanolmethylamine	Benzoylthebaol (49).
Thebaine methiodide	Sodium methylate	Tetramethylethylenediamine	Thebaol (22).
Do	Alkali	do	N-free portion not isolated, Freund (53), Roser (55).
Dihydrothebaine methyl ether	Hofmann degradation	Unidentified	Methylthebaol (35).
Phenyldihydrothebaine	do	Trimethylamine	Phenyldihydrothebenol (35).
Dichlorophenyldihydrothebaine	do	do	Dichlorophenyldihydrothebenol (82).

The more important degradations to phenanthrene derivatives

Compound	Method	Basic part	Nonbasic part
Phenyltetrahydrothebainine	do	do	Phenyltetrahydrothebenol (82).
Methylthebainone methohydroxide	Heat	do	N-free product not isolated (56).
Methylthebainone methine	Acetic anhydride	Ethanoldimethylamine	Dimethylmorphol (56).
Do	Sodium ethylate	Ethyldimethylamine	2 phenanthrene derivatives (56).
Dihydro-des-N-methyldihydrothebainone	Hofmann degradation		Thebenone (87).
Methyldihydrohydroxythebainone	do	Trimethylamine	Methyldihydrohydroxythebaone (83).
Thebenine methiodide	Alkali	do	Thebenol (53).
Dihydrothebenine dimethyl ether	Hofmann degradation	do	Methoxydihydrothebenol (84).
Dimethylthebenine methosulphate	Boiling alkali	do	3, 4, 8-Trimethoxy-5-vinylphenanthrene (57) (58) (59.)
Methethebenine methomethylsulphate	Alcoholic alkali	do	3, 4-Dimethoxy-8-ethoxy-5-vinylphenanthren (59) (60).
Dimethylmorphothebainemethine methiodide	Alkali	do	3, 4, 6-Trimethoxy-8-vinylphenanthrene (59) (61) (62).
Dimethylapomorphine	Hofmann degradation	do	3, 4-Dimethoxy-8-vinylphenanthrene (28) (29) (63) (64).
Dimethylapomorphine methine	Zinc dust distillation	Hydrogen cyanide, trimethylamine and ammonia.	Ethylphenanthrene (64).
Pseudomorphine methiodide methohydroxide	Acetic anhydride	Not isolated	Bis-(2, 2′)-3, 4-diacetylmorphol (65).
Dithebainone methine	do	do	Bis-(1, 1′)-3-methyl-4-acetylmorphol (65).
Desoxytetrahydro-α-methylmorphimethine methiodide.	Hofmann degradation	Trimethylamine	$C_{13}H_{16}O_2$ (66) (67).
Do	do	Not isolated	$C_{17}H_{20}O_2$? (66).
Diacetylhexahydro-ε-methylmorphimethine methiodide.	do	Trimethylamine	$C_{19}H_{24}O_4$ (66).
α-Methylmorphimethine methiodide	do	do	Methylmorphenol (11) (39) (68).
α-Methylmorphiethine methiodide	do	Ethylmethylpropylamine	Methylmorphenol (8).
Acetyl-α-methylmorphimethine	Heat	Not isolated	Methylmorphenol (69).
β-Methylmorphimethine methiodide	Hofmann degradation	Trimethylamine	Methylmorphenol (10) (69).
Do	Alcoholic potash	Not isolated	Morphenol (70).
β-Methylmorphimethine methyl ether methiodide	KOH in dilute alcohol	do	Morphenol (71).
γ-Methylmorphimethine methohydroxide	Heat	do	Methylmorphenol (72).
ε-Methylmorphimethine methiodide	Alcoholic potash	Trimethylamine	Morphenol (42).
ε-Methylmorphimethine methyl ether methohydroxide.	Heat	do	Methylmorphenol, ethylene and methyl alcohol (73) (74).
Piperidomethylmorphimethine methiodide	Alcoholic KOH	Not investigated	Phenolic substance, not morphenol (49).
Ethylmorphiethine methohydroxide	Heat	Methylethylpropylamine	Ethylmorphenol (9).
Tetrahydro-γ-methylmorphimethine methiodide	Hofmann degradation	Not isolated	$C_{17}H_{20}O_3$? (66); 13-vinyl-6-hydroxyoctahydromethylmorphenol (?).
Bromomethylmorphimethine methiodide	do	Trimethylamine	Bromomethylmorphenol (6) (8) (75).
Codeine sulphonic acid methohydroxide	Hot alkali	Tetramethylethylenediamine	Methoxymethylmorphenol sulphonic acid (?)(76).
Dihydrothebainemethine methohydroxide	Heat	Trimethylamine	6-Methoxy-13-vinyltetrahydromethylmorphenol (77) (78).
Chlorodihydrocodide	Hofmann degradation	do	Unidentified unstable product (85).
Dihydroisocodeine	do	do	$C_{17}H_{18}O_3$ (86).

Descriptive Part (Morphol and Morphenol)

MORPHOL, 3, 4-Dihydroxyphenanthrene, $C_{14}H_{10}O_2$, prep. by saponification of diacetylmorphol with alcoholic ammonia at 100° (1), or from treatment of α-methylmorphimethine with hydrogen chloride at 180° (38). Preparation from 3-phenanthrol-4-aldehyde, Barger (14); from phenanthrene-3, 4-quinone, Fieser (16). It cryst. from air-free water in an indifferent atmosphere in nearly colorless crystals of m. p. 143°; soluble in alkali, and very easily oxidized (1). It may be crystallized from ligroin (b. p. 80° to 90°), and sublimes in high vacuum at 130° (14). Acetylation, methylation, Barger (14). DIACETYLMORPHOL, $C_{14}H_8(OCOCH_3)_2$, prep. by heating morphine methiodide (1) or α-isomorphine methiodide (2) with acetic anhydride. It cryst. in white needles from ether, m. p. 159°, sublimes undecomposed. It is insoluble in water, acids or alkali (1). It oxidizes with chromic acid to DIACETYLMORPHOLQUINONE, $C_{18}H_{12}O_6$, yellow needles from gl. acetic acid, of m. p. 196° (1) (3). It has also been prepared from phenanthrenequinone (15). The Azine melts at 215° to 218° (3). By saponification, MORPHOLQUINONE is obtained (3) which cryst. in brownish needles from alcohol, and dyes mordanted cotton (15).

METHYLMORPHOL, 3-Methoxy-4-hydroxyphenanthrene, $C_{15}H_{12}O_2$, prep. by saponification of the acetyl derivative (1) or directly by treatment of α-methylmorphimethine with dry HCl (38), or from chloromethylmorphimethine with alcohol at 100° (44). It cryst. in needles of m. p. 62° to 63°, and yields a Picrate of m. p. 150° (44). METHYLMORPHOL DIMETHYLAMINOETHYL ETHER is not crystalline, but gives a Hydrochloride m. p. 214° to 215°, Picrate, m. p. 189°, and Methiodide, m. p. 196° to 198° (79). ACETYLMETHYLMORPHOL, $C_{17}H_{14}O_3$, obtained in numerous acetolysis reactions of codeine derivatives. (See table, p. 285.) Cryst. from alcohol in needles, m. p. 131°, sublimes undecomposed. It yields, on oxidation ACETYLMETHYLMORPHOLQUINONE (7) (10), yellow needles from acetic acid, m. p. 205° to 207°. BENZOYLMETHYLMORPHOL is not crystalline, but yields a Quinone, yellow needles of m. p. 228°.

DIMETHYLMORPHOL, 3, 4–Dimethoxyphenanthrene, $C_{16}H_{14}O_2$. Prep. by methylation of morphol (14) or methylmorphol (13), or from degradation of methyldesoxycodomethine (50) or methylthebainone methine (56), synthesized by Pschorr (12). It cryst. in white leaflets from methyl alcohol, m. p. 44°, boils at 298° to 303°/112 mm., and yields a Picrate of m. p. 104° to 105° (13). DIBROMODIMETHYLMORPHOL melts at 125° and is used to characterize dimethylmorphol (13).

ACETOMETHYLMORPHOL, $C_{17}H_{14}O_3$, prep. from aceto-β-methylmorphimethine with sodium ethylate at 150°. It cryst. from alcohol in needles of m. p. 161° to 162°; Semicarbazone melts at 220°. The acetyl group is probably in the 1-position.

BROMOMETHYLMORPHOL, isolated as the acetyl derivative, $C_{17}H_{13}O_3Br$, from acetolysis of bromomethylmorphimethine (46) or of hydroxydihydrobromomethylmorphimethine (47). Cryst. from methyl alcohol in needles of m. p. 166°.

MORPHENOL, 3-Hydroxy-4, 5-phenanthrylene oxide, $C_{14}H_8O_2$, prep. by degradation of β-(70) (71), γ- (72), or ϵ-methylmorphimethine (42) quaternary hydroxides with alcoholic potash, or by heating methylmorphenol (7) (11) or ethylmorphenol (9) with hydriodic acid. Best preparative method, Vongerichten (11) (80). It is obtained in quantitative yield from bromomethylmorphenol with hydriodic acid (6). Morphenol is converted to phenanthrene by distillation over zinc dust (7); to trihydroxyphenanthrene by fusion with KOH (18). Morphenol cryst. in nearly colorless needles from ether, or alcohol (6) m. p. 145° (10). ACETYLMORPHENOL, $C_{16}H_{10}O_3$, white needles of m. p. 140° (6) (10) oxidation (10) (11). It reacts with bromine to give a Bromoacetylmorphenol, $C_{16}H_9O_3Br$, white needles of m. p. 208° (11) (75). BENZOYLMORPHENOL, $C_{21}H_{12}O_3$, colorless crystals from acetic acid, m. p. 123° (6) (11).

METHYLMORPHENOL, $C_{15}H_{10}O_2$, crystals from alcohol, m. p. 65°, distills undecomposed (1); molecular weight determination, Vongerichten (81). It is obtained in the Hofmann degradation of a large number of substances in the morphine series (see table, p. 285); preparative method, Vongerichten (10) (11) (80). Distilled with zinc dust it yields phenanthrene (1) (81). It yields with bromine a tetrabromo derivative, $C_{15}H_6O_2Br_4$, m. p. 290° (81). When acetylmorphenol is brominated, saponified and then methylated, β-BROMOMETHYLMORPHENOL, $C_{15}H_9O_2Br$, needles of m. p. 124° is formed; it can also be obtained by direct bromination of methylmorphenol in CS_2 at 0° (75). By degradation of bromomethylmorphimethine, α-BROMOMETHYLMORPHENOL is obtained, white needles of m. p. 123° (6) (75). The isomers behave differently toward oxidation or further bromination.

ETHYLMORPHENOL, $C_{16}H_{12}O_2$, from degradation of codethyline. It melts at 59°, and may be distilled (9).

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THEBAINE

Thebaine was discovered in 1835 by Pelletier and Thiboumery (1) (2) who believed it to be an isomer of morphine, and gave it the name "Paramorphine." The name thebaine was introduced by Couerbe (3) (4) (*cf.* Kane (5)). The correct composition of the base, corresponding to the formula $C_{19}H_{21}O_3N$ was first determined by Anderson (6) (7), whose analyses were later confirmed by those of Hesse (8) and Beckett and Wright (9).

The separation of thebaine from opium extract usually takes place after morphine, codeine, narcotine, and papaverine have been removed. The alcoholic mother liquor from which narcotine and papaverine have crystallized is concentrated and taken up in acetic acid. Basic lead acetate is added to alkaline reaction, whereby narcotine and resinous materials are precipitated; the filtrate is freed from lead with sulphuric acid, and the crude thebaine precipitated with ammonia (7).

Hesse (8) treated the mother liquors from morphine-codeine separation with excess of alkali, and dissolved the heavy precipitate in dilute acetic acid; narcotine and most of the other alkaloids remain undissolved. By addition of tartaric acid to the acetic acid solution, the thebaine was precipitated as the sparingly soluble acid tartrate. Plugge's (10) method makes use of thebaine salicylate. A review of these separations, as well as the description of a new method, which depends upon the differences in basicity of the opium alkaloids, is given in the discussion by Kanewskaja (11); see also Ishikawa (12). Gulland and Robinson (13) have observed cryptopine as an impurity in commercial thebaine.

Thebaine occurs chiefly in *Papaver somniferum*, where it appears to be the last alkaloid formed by the growing plant (14). The amounts found in opium vary from 0.2% to 0.3% (15) to 0.8% (16) or 1%. Gadamer and Klee (17) (18) observed that thebaine is present in *Papaver orientale* during the period of growth, but appears to be changed to the isomer, isothebaine, as the plant withers. Isothebaine is an isoquinoline derivative of the apomorphine type.

Thebaine crystallizes from alcohol in shining leaflets, from dilute alcohol in rectangular plates (6), often associated in tufts more or less radiating from a center (Deane and Brady (19), illustration). Thebaine melted and cooled forms highly refracting biaxial crystals; at low temperatures it crystallizes in two kinds of spherulites (20). Thebaine crystallized from solvents has the density 1.305 (1.282) (21), the refractive indices 1.63 and 1.69 (14), and melts at 193° (8).

Blyth (22) observed sublimation of thebaine at 135° under atmospheric pressure in needlelike crystals; at higher temperatures, cubes and prisms were formed. Sublimation and microsublimation in vacuum are described by Kempf (23) and Heiduschka (24). Vacuum-sublimed thebaine melts at 192.5° (196.2° corr.) (23).

The thermochemistry of thebaine has been studied by Leroy (25) (26) who found the heat of combustion at constant volume to be 2439.9 Cal., at constant pressure 2441.8 Cal.; this is in good agreement with the values expected of a dimethyl ether of morphine less two hydrogen atoms.

The absorption spectrum of thebaine was investigated by Hartley (27) and Kitasato (28), the ultraviolet spectrum by Steiner (29).

Thebaine is levorotatory; in 97% alcohol, Hesse (30) found $[\alpha]_D^{15} = -218.64°$ (p = 2). The rotatory power is affected but little by change in concentration, but decreases rapidly with rise in temperature. In chloroform, $[\alpha]_D^{22.5} = -229.5°$ (p = 5). Thebaine hydrochloride in aqueous solution gives the value $[\alpha]_D^{15} = -163.66°$ (p = 2).

Thebaine is a strong monoacid base, whose salts with strong acids are stable and neutral in reaction. An aqueous suspension of the base turns litmus blue (8), or helianthin to yellow; the aqueous suspension does not affect phenolphthalein, but addition of water to alcoholic thebaine solution containing phenolphthalein gives a rose color (26).

Thebaine is soluble in alcohol, ether, benzene, chloroform (2) (7) (8), aniline, pyridine, or piperidine (31), practically insoluble in water, ammonia, or alkalies (6). One part of thebaine dissolves in 140 parts of ether (10°) (8) in 10 parts of cold alcohol (2), in 59 parts of amyl alcohol (32), 19 parts of benzene (32), 18 parts of chloroform, or 11.1 parts of pyridine (20° to 25°) (33); it is insoluble in petroleum ether (34).

The following reactions have been proposed for the identification or detection of thebaine:

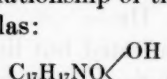
Thebaine color and precipitation tests

Reagent	Reaction	Observer
Conc. H_2SO_4	Red, becoming yellow	Hesse (8); Reichard (35).
Conc. H_2SO_4 containing HNO_3.	Red, yellow in thin layers	Couerbe (3).
Conc. HNO_3	Colorless, 10 min. yellow, 60 min. dark yellow	Reichard (35).
Conc. HCl	Yellow to greenish	Do. (35).
Marquis' reagent	Red	Pfister (36).
Fröhde's reagent	do	Do. (36).
Mandelin's reagent	do	Do. (36).
2% aqueous furfurol	Transient red	Do. (36).
Magnol (basic magnesium hypochlorite)	Alkaloid in 3 c. c. acetic acid cont. 0.2% magnol, and layered onto conc. H_2SO_4, forms a red ring; after 24 hours the test shows a layer of the color Scharlach G over a yellow zone over a broad Scharlach G ring over a yellow layer.	David (37).
$ZnCl_2$ in dil. HCl	Reagent is added to the dry hydrochloride, and evaporated on porcelain to dryness on the water bath: Yellow.	Jorissen (38); Czumpelitz (39).
K_2CrO_4	Precip. scales of $B_2H_2CrO_4$	Plugge (40) (41).
$K_2Cr_2O_7$	Precip. needles of $B_2H_2Cr_2O_7$	Plugge (40).
$K_3Fe(CN)_6$ or $K_4Fe(CN)_6$	Precip. of hydroferri- or hydroferro-cyanide	Plugge (40) (41).
PbO_2, H_2SO_4	Thebaine is boiled with PbO_2 in acetic acid, filtered, and the filtrate treated with excess conc. H_2SO_4: filtrate is orange-red, turning golden-yellow when the H_2SO_4 is added.	Deér (42).
Iodine chloride	Yellow precip. which gives off iodine vapor on boiling in water.	Dittmar (43).
$SbCl_3$	Weak blue color, which disappears on warming	Smith (44).

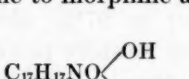
The sensitivity of thebaine to a large number of precipitants is given by Kerbosch (14). Wagenaar (45) claims that precipitation as the free base is more delicate than as the salicylate, acid tartrate, or periodide.

The problem of the structure of thebaine was first attacked by Howard and Roser (46) (47), who showed that the base contained

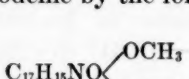
two methoxyl groups and a tertiary-linked nitrogen. They expressed the relationship of thebaine to morphine and codeine by the following formulas:



Morphine

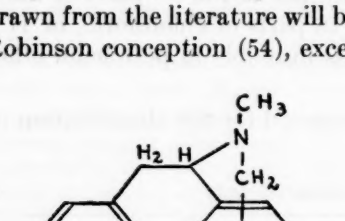


Codeine

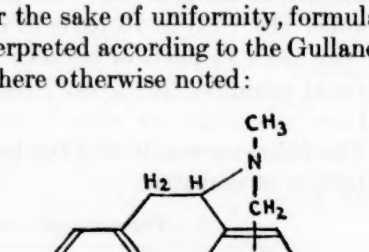


Thebaine

Further notable advances in our knowledge of thebaine were made shortly thereafter by Freund (48) (49) (50) (51), in his studies on the degradation and rearrangements of the base. After the establishment of a relationship between codeinone and thebaine by Knorr (52) (53) (see p. 257), the results of the thebaine researches became applicable to the structural problem of morphine and codeine; the evidence which has led to the proposal of the structural formulas below will therefore be discussed in the section devoted to the structure of morphine and codeine (p. 336). For the sake of uniformity, formulas drawn from the literature will be interpreted according to the Gulland-Robinson conception (54), except where otherwise noted:

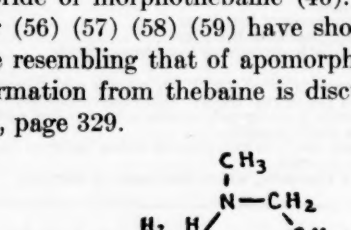


Thebaine
(Knorr-Wieland)



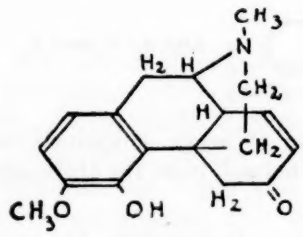
Thebaine
(Gulland and Robinson)

Thebaine dissolves in concentrated hydrochloric acid to give an orange-red halochromic solution, which no longer contains any trace of thebaine (55). If this solution is heated to 100° in a closed vessel, the red color disappears, and crystals of a new substance separate, the acid hydrochloride of morphothebaine (46). The researches of Knorr and Pschorr (56) (57) (58) (59) have shown morphothebaine to have a structure resembling that of apomorphine; the mechanism proposed for its formation from thebaine is discussed in the section on morphothebaine, page 329.

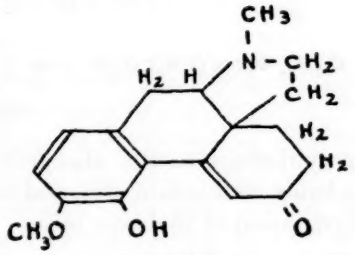


Morphothebaine

If the halochromic hydrochloric acid solution of thebaine mentioned above is reduced with stannous chloride (Pschorr (60)), a phenolic ketone, thebainone, results. The structure of thebainone is still in doubt (see p. 308); the two most recent proposals are given below.

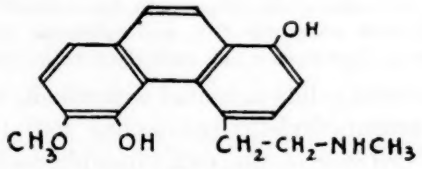


Thebainone
(Gulland and Robinson (54) (61))



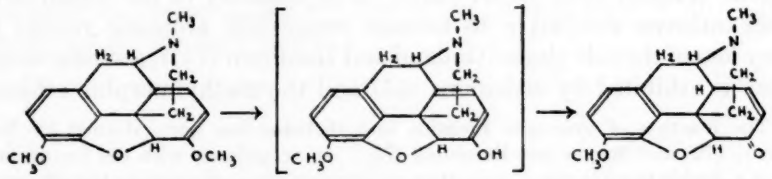
Thebainone
(Schöpf and Borkowsky (55))

When thebaine is warmed with dilute hydrochloric acid, a phenolic secondary amine, thebenine (8) is formed. The determination of the structure of thebenine by Freund (48) (50) (51) and Pschorr (58) (62) and the mechanism of its formation from thebaine are discussed on page 321.



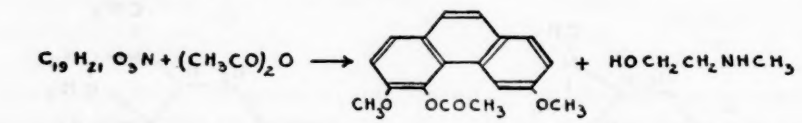
Thebenine

When thebaine is heated with dilute (normal) sulphuric acid, it is converted in large part to alkali-soluble products of unknown nature; about 5% yield of the ketone codeinone, one of the oxidation products of codeine (see p. 247) is obtained. This is believed to be formed by hydrolysis of the enol-ether methoxyl on C-6 of thebaine (53).



The hydrolysis of thebaine to codeinone was conceived by Knorr (53) to be the first step in the formation of thebenine and morphothebaine, for codeinone is convertible to these two bases under the action of acids. Codeinone can be reduced to codeine (63) (64), and the changes thebaine ⟶ codeinone ⟶ codeine represent therefore a transformation of thebaine to codeine. The reverse process has not been realized.

In marked contrast to codeine, thebaine is broken down by acetic anhydride (*cf.* Beckett and Wright (9)) into a nitrogen-free product, acetylthebaol, and ethanolmethylamine (49); the latter is, of course, obtained in the form of its acetyl derivative:



Acetylthebaol results also from the action of acetic anhydride on thebaine methiodide (49), and the phenol, thebaol, from the Hofmann degradation of thebaine (65).

Thebaol, on distillation with zinc dust, yields phenanthrene. The relationship of thebaol to phenanthrene is further shown by oxidation; acetylthebaol is converted by the action of chromic acid into acetylthebaolquinone (50), whose structure as 3, 6-dimethoxy-4-acetoxyphenanthrene-9, 10-quinone was established through synthesis by Pschorr, Seydel, and Stöhrer (66). Thebaol methyl ether [1] was likewise synthesized by the same investigators.

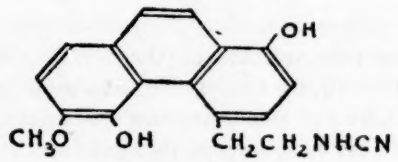
Thebaine is split by benzoyl chloride at 0°, yielding benzoylthebaol and ethanolmethylamine (69).

Certain compounds in the codeine series have been degraded to thebaol derivatives by acetolysis: bromacetoxydihydro-a-methylmorphimethine is broken down to acetylthebaol by acetic anhydride (70), and codeinone yields with the same reagent a phenanthrene derivative which methylates to methylthebaol (52).

When thebaine methiodide is heated with alkali, it is split directly to thebaol and tetramethylethylenediamine (50) (65) without the formation of a substance of the methylmorphimethine type. Thebaine methiodide is degraded even on heating with alcohol alone (165°), to thebaol, dimethylaminoethyl ethyl ether, and dimethylamine. The unusual ease with which complete loss of the ethanamine side chain from thebaine takes place is undoubtedly connected with its nature as a tetrahydrophenanthrene derivative, in contrast to morphine and codeine, which are derived from a hexahydrophenanthrene (Freund (50), Knorr (52)). The tendency of the tetrahydrophenanthrene derivative to become completely aromatic results in easy loss of the side chain (Gulland and Robinson (71)); a similar tendency is exhibited by codeinone (65) and the methylmorphimethines.

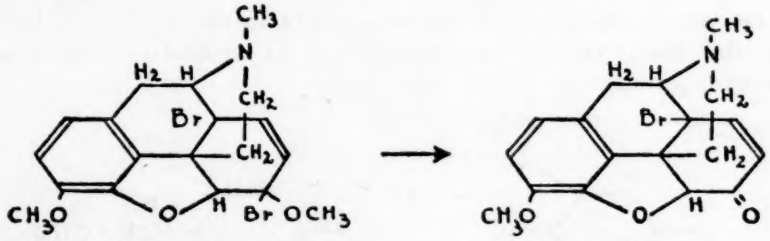
The reaction of cyanogen bromide and thebaine has been studied by Von Braun (72) and Speyer and Rosenfeld (73). In accordance with the known fact that a double bond in the β, γ-position to nitrogen often so weakens the nitrogen-carbon bond that the nitrogen ring breaks before replacement of N-methyl by the CN group takes place, thebaine was found to yield a norcyanothebenine. The first step in the transformation is believed to be the formation of thebenine, whose N-methyl group is then replaced by CN in normal fashion (73).

[1] This compound is obtained by methylation of thebaol (67) or directly from thebaine by degradation (68) of the methyl ether methiodide of that dihydrothebaine which is formed when thebaine is reduced with sodium and alcohol (51) (p. 297).



Norcyanothebenine

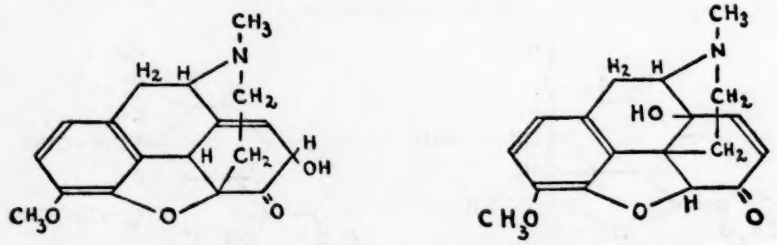
The action of halogens on thebaine was investigated without result by Anderson (7) at an early date. Later work (Freund (74)) showed that bromine acts on thebaine to split out a methyl group, with formation of a bromine-containing ketone, bromocodeinone. Schöpf (75) considers it probable that 1, 4-addition of bromine (at C-6 and C-14) takes place, that Br on C-6 is then substituted by OH, and methyl alcohol is split off. The reactions of bromocodeinone are considered in detail on page 252.



Thebaine Dibromide (hypothetical) Bromocodeinone

Schmidt (76) states that thebaine reacts with hydrogen sulphide, but he was unable to isolate any definite product.

Cold 30% hydrogen peroxide acts on thebaine in the normal way to give an amine oxide derivative, which is converted back to thebaine by reducing agents (77) (78). If, on the other hand, a boiling solution of thebaine in acetic acid is treated with 30% hydrogen peroxide a hydroxy-ketone, hydroxycodeinone, is obtained (79) (80) (81). This is believed to be formed through addition of a molecule of hydrogen peroxide to thebaine, followed by loss of methyl alcohol (80). (*Cf.* formation of bromocodeinone.)

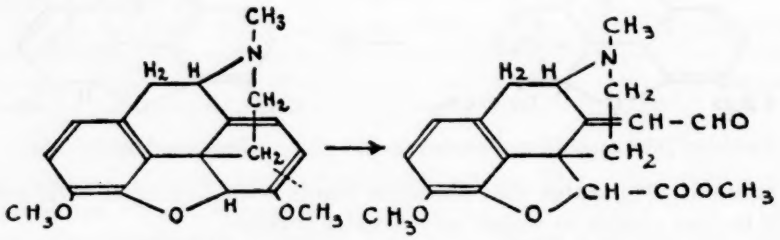


Hydroxycodeinone (Freund) Hydroxycodeinone (Robinson)

The chemistry of hydroxycodeinone is considered in detail on page 254.

Long continued action of boiling 30% hydrogen peroxide on thebaine in neutral solution results in the formation of a new base, dehydrothebaine, containing two hydrogen atoms less than thebaine (80). It is apparently not phenolic, and still contains two methoxyl groups; nothing further is known of its structure.

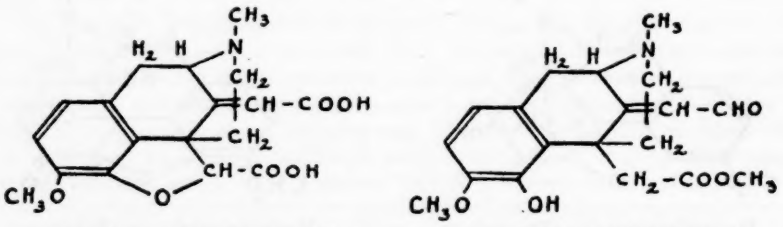
The behavior of thebaine with ozone was first studied by Pschorr and Einbeck (82) (83), who isolated a product $C_{19}H_{21}O_5N$, containing two oxygen atoms more than thebaine, which was named thebaizone. They established the presence of a carbonyl and methyl ester grouping, which were considered to have been formed through ozonolysis of a double bond in the hydroaromatic ring of thebaine. Faltis (84), in support of his thebaine formula (p. 345), sought to prove by the Angeli and Rimini nitroxyl reaction that thebaizone contains no aldehyde grouping; his experiment was inconclusive. The recent investigation of Wieland and Small (85) has shown the view of Pschorr to be correct: ozonolysis of thebaine results in the rupture of the 6, 7-double bond, yielding the methyl ester of an acid containing an aldehyde group.



Thebaine α-Thebaizone

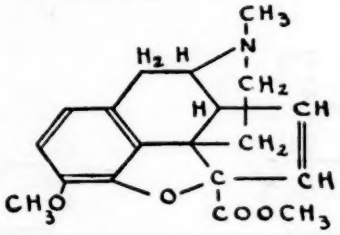
Thebaizone, as an ester, is saponified by alkalies (82) to a monobasic aldehyde acid, thebaizonic acid (85). When warmed with hydrochloric acid, thebaizonic acid adds a molecule of water, giving the hydrochloride of hydroxydihydrothebaizonic acid. Hydrogen peroxide oxidizes thebaizone, with simultaneous hydrolysis of the ester group, to a dibasic acid (85) (*cf.* Speyer (86)), thebaizone dicarboxylic acid; by this reaction, as well as by the color given with Schiff's reagent, the presence of the aldehyde group in thebaizone is demonstrated.

Hydrogenation of thebaizone in the presence of platinum results in opening the ether grouping, to the phenolic dihydrothebaizone.



Thebaizone Dicarboxylic Acid Dihydrothebaizone

Reduction of thebaizone with aluminum amalgam leads to the formation of a yellow compound containing one oxygen atom less than thebaizone, desoxythebaizone. It is believed to contain a new, unsaturated ring, and can be hydrogenated catalytically to a dihydrodesoxythebaizone (85).

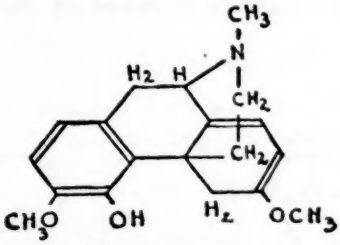


Desoxythebaizone

α-Thebaizone rearranges under the influence of heat to an isomer, β-thebaizone which differs from α-thebaizone in the spatial arrangement of the groups attached to the doubly linked C-8; it reduces to the already-mentioned desoxythebaizone (85).

Degradation of thebaizone and its derivatives to nitrogen-free products was unsuccessful.

Thebaine is reduced by sodium and alcohol with addition of two hydrogen atoms to a phenolic dihydrothebaine (51) (103), which is undoubtedly formed by reductive scission of the ether bridge.



Dihydrothebaine

The behavior of this dihydrothebaine toward catalytic hydrogen has not been described (*cf.* Freund (104)).

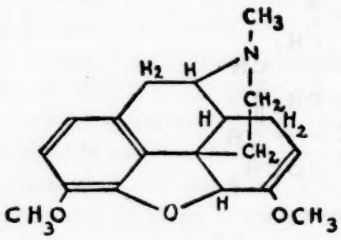
Dihydrothebaine methiodide is quite stable towards alkali. When boiled with sulphurous acid, it is converted to the hydriodide of an isomer of dihydrothebaine, isodihydrothebaine (51),

$$\begin{matrix} CH_3O \\ HO \end{matrix}\!\!\rangle C_{16}H_{13}ON(CH_3)_2 \cdot HI$$

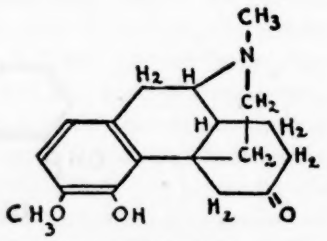
Dihydrothebaine is changed by cold dilute hydrochloric acid into an ill-defined substance to which the name isocodeine was given (51). The name isocodeine was claimed at a later date for one of the stereoisomers of codeine (p. 215).

The catalytic hydrogenation of thebaine in the presence of palladium or platinum proceeds in a complicated way. The reaction was first studied by Oldenberg (87) (88) in 1911, who designated the amorphous, obviously impure product as "tetrahydrothebaine." (*Cf.* Von Braun (72).) In later studies, Freund and Speyer (89) and Skita (90)

succeeded in isolating the well-characterized nonphenolic dihydrothebaine of m. p. 162° to 163°. When colloidal palladium in acetic acid is used as the catalyst, the chief product appears to be the phenolic dihydrothebainone (90), which is discussed in the section on thebainone, p. 309.

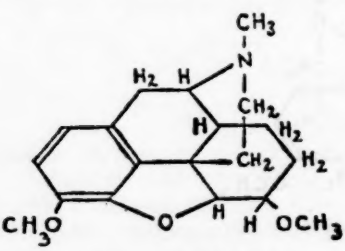


Dihydrothebaine

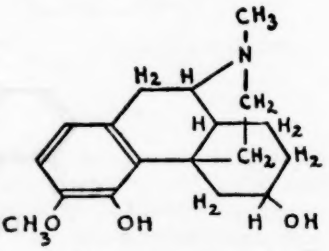


Dihydrothebainone

The hydrogenation of thebaine has recently been thoroughly investigated by Schöpf and Winterhalder (91), who found in addition to the products mentioned above, a third base, tetrahydrothebaine. This proved to be identical with dihydromorphine dimethyl ether. According to Boehringer's patent (92) tetrahydrothebaine is formed in exceptionally high yields when a platinum oxide catalyst is used. With platinum catalysts, the appearance of a fourth base, dihydrothebainol (p. 314) has also been observed (*cf.* Skita (90)).



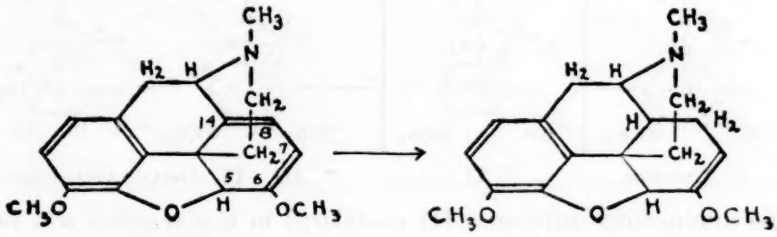
Tetrahydrothebaine
(Dihydromorphine dimethyl ether)



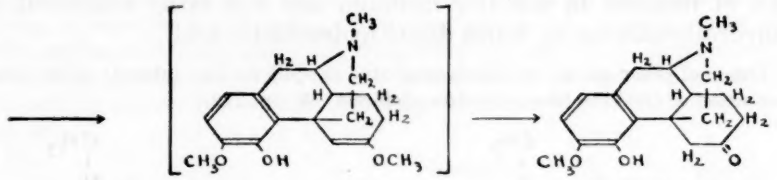
Dihydrothebainol

The mechanism of thebaine hydrogenation was formulated by Schöpf (91) as follows: The various products of the reaction may be conceived as resulting from addition of hydrogen in different ways to thebaine. When addition takes place, 1, 2- to C-14 and C-8 of thebaine, dihydrothebaine results, which under mild conditions is not further reduced, but under vigorous treatment goes to dihydrothebainone through scission of the ether bridge; in this respect it is comparable to pseudo- and allopseudo-codeine. The grouping $-O-\underset{|}{CH}-CH=CH-$ present in dihydrothebaine is analogous in certain respects to a conjugated system of double bonds $-CH=CH-CH=CH-$, and it seems probable that in the case of dihydrothebaine addition of hydrogen takes place to this system in the 1, 4-manner when

forced; in the postulated intermediate phenolic product, hydrolysis of the enol ether group takes place faster than does hydrogenation of the double bond [2] and dihydrothebainone results.



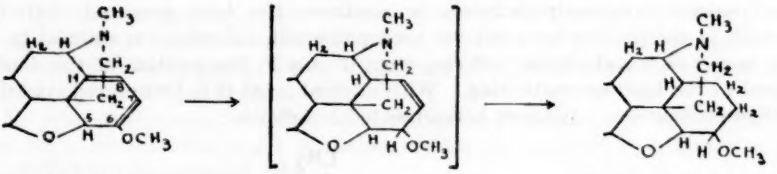
Thebaine Dihydrothebaine



Dihydrothebainone

The location of the double linkage in Ring III of dihydrothebaine in the 6, 7-position finds confirmation in the behavior of the methoxyl as an enol ether group (89) and in the ozonolysis experiments of Wieland and Small (85). Dihydrothebaine yields with ozone the methyl ester of an aldehyde acid, isodihydrothebaizone. (Compare the ozonolysis of thebaine, p. .266)

When addition of hydrogen to thebaine takes place in the 1, 4-manner, at C-6 and C-14, the end-product is tetrahydrothebaine (91).

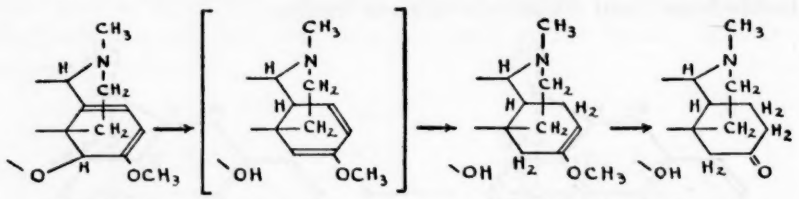


Thebaine Tetrahydrothebaine

Dihydrothebainone is obtained in considerable amounts from the reduction of thebaine, even under mild conditions. It is not formed through reduction of dihydrothebaine (which takes place only when the hydrogenation is forced), since the absorption of hydrogen comes to a complete stop while much dihydrothebaine is still present.

[2] Hydrolysis of enol ethers is accelerated on the catalyst surface, as was shown by Wieland and Garbsch, Ber. 59, 2490 (1926).

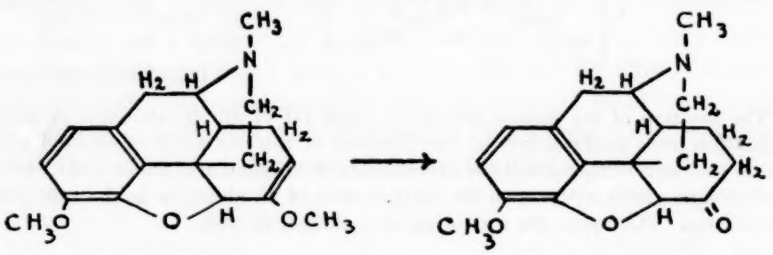
Schöpf believes that the dihydrothebainone is formed in this case directly from thebaine, through primary 1, 6-addition of hydrogen:



I. Thebaine II III IV. Dihydrothebainone

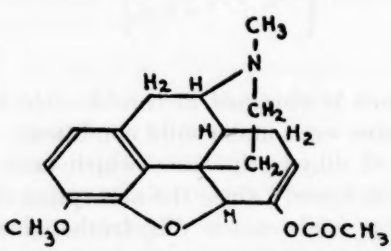
The intermediate substance III postulated in this reaction was isolated by Wieland and Kotake (93), as the product from hydrogenation of thebaine in acid-free medium, and was easily converted to dihydrothebainone by warm dilute hydrochloric acid.

The enol ether group of dihydrothebaine is split by hot mineral acids, with formation of the keto base, dihydrocodeinone (89) (p. 249).



Dihydrothebaine Dihydrocodeinone

By saponification of the enol ether group of dihydrothebaine and acetylation, acetylodemethylodihydrothebaine, or acedicon, has been prepared (94); the details of the process have not yet been published. Acedicon is claimed to be an isomer of acetylcodeine, differing from it only in the position of the double bond in the hydroaromatic ring. With mineral acids it is hydrolyzed, yielding dihydrocodeinone. Acedicon is represented as follows:

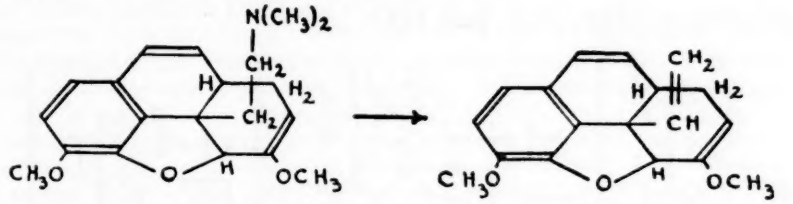


Acetylodemethylodihydrothebaine (Acedicon)

Dihydrothebaine reacts with cyanogen bromide to give cyanonordihydrothebaine (89).

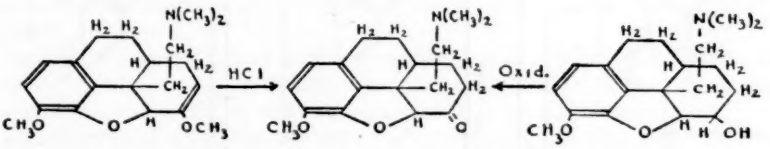
The Hofmann degradation of dihydrothebaine proceeds with the formation of des-N-methyldihydrothebaine (dihydrothebaine methine), containing a new double linkage in the 9, 10-position. Des-N-methyldihydrothebaine methiodide

splits with alkali into trimethylamine and a phenanthrene derivative, 6-methoxy-13-vinyltetrahydromorphenol methyl ether (89) (95). Hydrolysis and reduction products from this are described on p. 304.



Des-N-Methyldihydrothebaine 6-Methoxy-13-vinyltetrahydromorphenol Methyl Ether

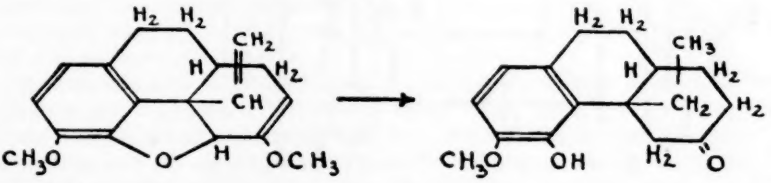
Des-N-methyldihydrothebaine hydrochloride, when treated with hydrogen and palladous chloride adds one molecule of hydrogen at the 9, 10-unsaturation, giving dihydro-des-N-methyldihydrothebaine; with hot hydrochloric acid this splits at the enol ether group (*cf.* dihydrothebaine above) to dihydro-des-N-methyldihydrocodeinone, which has also been prepared by oxidation of tetrahydromethylmorphimethine and by hydrogenation of des-N-methyldihydrocodeinone (96).



Des-N-methyldihydrothebaine, in a similar manner, is hydrolyzed by acids to des-N-methyldihydrocodeinone, identical with the product obtained from degradation of dihydrocodeinone (96).

Both the 4, 5-ether bridge and 9, 10-double linkage of des-N-methyldihydrothebaine can be hydrogenated using Skita's catalyst in very dilute acetic acid, whereby simultaneous hydrolysis of the enol ether group takes place; the product is dihydro-des-N-methyldihydrothebainone, identical with the hydrogenation product from des-N-methyldihydrothebainone (96) (from degradation of dihydrothebainone (89), p. 314).

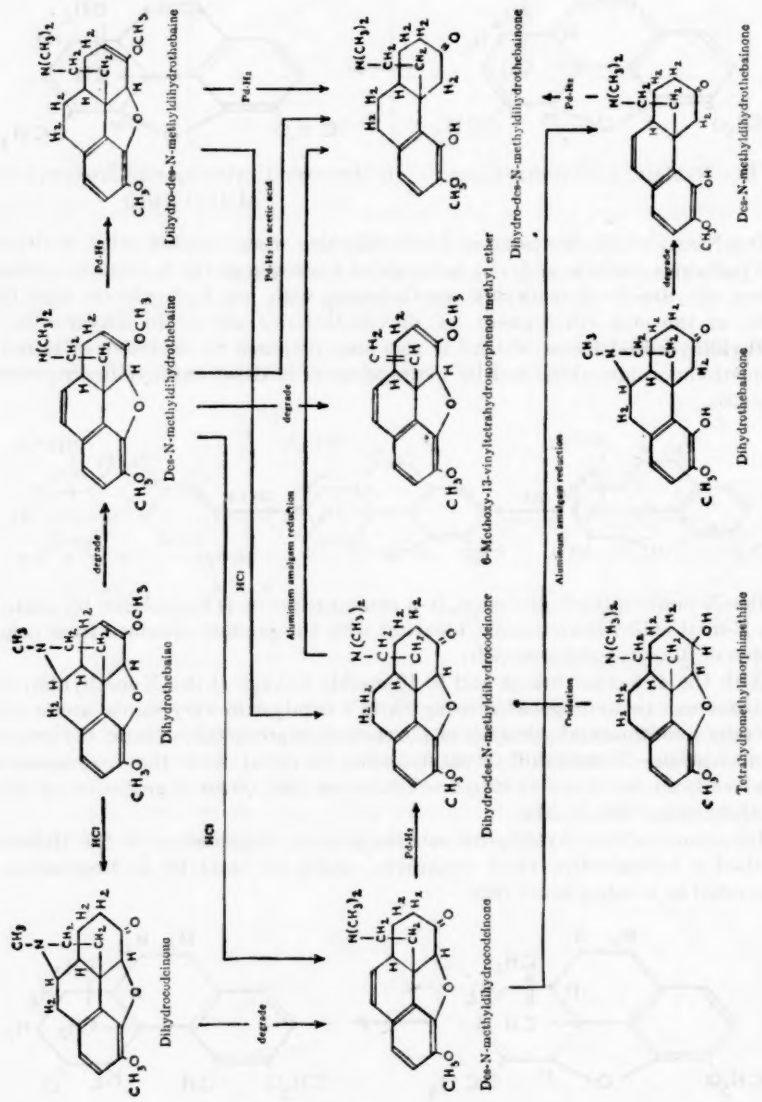
Dihydro-des-N-methyldihydrothebaine gives on degradation by the Hofmann method a nitrogen-free vinyl derivative, which on catalytic hydrogenation is converted to a keto-phenol (96).



If the hydrogenation is carried out in the absence of acid, a phenol which still contains the ether group results (93).

Thebaine reacts with phenyl magnesium bromide, yielding an exceedingly stable phenolic base containing a phenyl group (68) (103) (105). This compound, phenyldihydrothebaine, is considered in a separate section (p. 332).

Tetrahydrothebaine has been only very slightly investigated. With demethylating agents, as hydriodic acid or aluminum chloride it is converted quantitatively to dihydromorphine (92). See dihydromorphine dimethyl ether, page 149.*



Descriptive Part (Thebaine)

THEBAINE: $B=C_{19}H_{21}O_3N$. —HYDROCHLORIDE, $B\cdot HCl+H_2O$, rhombic prisms from alcohol, sol. at 10° in 15.8 parts of water (6) (7) (8). Thermochemical data, Leroy (26); $[\alpha]_D^{22.5}=-163.63°$ (water, p=2) (30). —PLATINICHLORIDE, $(B\cdot HCl)_2PtCl_4+2H_2O$, is an amorphous precipitate, changing to orange prisms (7) (8).

*See Appendix, p. 336.

—MERCURICHLORIDE, white cryst. precip. (7). —SULPHATE, white crystals (7). —OXALATE, $B_2 \cdot C_2H_2O_4 + 6H_2O$, prisms, soluble in 9.7 parts of water at 10°, soluble in alcohol, insoluble in ether (8). —BINOXALATE, $B \cdot C_2H_2O_4 + H_2O$, colorless prisms, soluble in 44.5 parts of water at 20°. —TARTRATE, amorphous, soluble in water or alcohol. —BITARTRATE, $B \cdot C_4H_6O_6 + H_2O$, white prisms, soluble in hot alcohol or hot water, soluble in 130 parts water at 20°. —HYDRIODIDE, colorless prisms, very soluble in water (8). —HYPOSULPHITE, white prisms, soluble in cold water. —MECONATE, $B_2 \cdot C_7H_4O_7 + 6H_2O$, prisms from alcohol, soluble in 304 parts of water at 20°. —CHROMATE, $B_2 \cdot H_2CrO_4$, yellow prisms, unstable (8) (40). —DICHROMATE, $B_2 \cdot H_2Cr_2O_7$, needles (40). —HYDROFERROCYANIDE, $B_4 \cdot H_4Fe(CN)_6$ (40). —HYDROFERRICYANIDE, $B_6 \cdot H_6Fe_2(CN)_{12}$ (40). —SALICYLATE, $B \cdot C_7H_6O_3$, crystals soluble in 753 parts of water (97). —PICRATE, crystallized from 50% alcohol, sinters 201°, m. at 217° (corr.) (98).

THEBAINE METHIODIDE: $B \cdot CH_3I$, cryst. from alcohol in prisms with one molecule C_2H_5OH, sol. in water (46). Conversion to acetylthebaol and thebaol, Freund (50), Knorr (65). —ETHIODIDE, $B \cdot C_2H_5I$, needles from alcohol (46). —METHOMETHYLSULPHITE, is crystalline and is converted by the action of KBr to the METHOBROMIDE (99).

THEBAINE-N-OXIDE, prep. by the action of 30% H_2O_2 on thebaine in neutral solution at 100°; isolated as the HYDROCHLORIDE, $C_{19}H_{21}O_4N \cdot HCl$, colorless needles from alcohol or water, decomp. at 238° to 239°. The free base is poorly crystalline, and melts unsharp at about 80°; it regenerates thebaine with sulphurous acid (77).

BROMOTHEBAINE: $C_{19}H_{20}O_3NBr$, amorphous reddish precip. obtained from the action of bromine-water on thebaine in hydrobromic acid solution. The TETRABROMIDE, $C_{19}H_{20}O_3NBr \cdot Br_4$ is an amorphous orange precipitate (46).

DIHYDROTHEBAINE (Phenolic) (51): $C_{19}H_{23}O_3N$, prep. by reduction of thebaine with sodium in ethyl alcohol. Purified by slow precip. from benzene with ligroin, or by recryst. from ethyl acetate; quadratic prisms, softening at 150°, melting at 154°. Soluble in alkali, and exceedingly stable toward it. The METHIODIDE cryst. from alcohol in 4-sided prisms of m. p. 155° to 160°, $C_{19}H_{23}O_3N \cdot CH_3I + C_2H_6O$; from water it cryst. in needles of m. p. 75° to 80°, with 3 molecules of crystal-water. The methiodide is converted by hot sulphurous acid to ISODIHYDROTHEBAINE HYDRIODIDE, $C_{19}H_{23}O_3N \cdot HI$, crystals from hot water, m. p. 230° to 235°. The corresponding base, ISODIHYDROTHEBAINE, liberated from the hydriodide by ammonia and crystallized from ligroin-benzene m. at 138°. Its Methiodide, cryst. from water, m. at 210° to 215°, and degrades to trimethylamine and a nitrogen-free product which could not be isloated. Dihydrothebaine, with cold dil. HCl, gives a poorly defined substance which was named ISOCODEINE (51) (not to be confused with the isocodeine from hydrolysis of chlorocodide, p. 224). Dihydrothebaine methiodide methylates to DIHYDROTHEBAINE METHYL ETHER METHIODIDE, $C_{20}H_{25}O_3N \cdot CH_3I$, cryst. from alcohol, m. p. 192°, which can be degraded to methylthebaol (68).

DIHYDROTHEBAINE: $C_{19}H_{23}O_3N$, prep. by catalytic reduction of thebaine with palladium and hydrogen (Freund and Speyer (89), Skita (90), Wieland and Kotake (96), Gulland and Robinson (13)). Schöpf (91) studied the effect of temperature and pH on the yield. Prismatic plates from alcohol, m. p. 162° to 163° (89), colorless prisms from ethyl acetate (96), insol. in alkali. $[\alpha]_D^{20} = -266.86°$ (benzene, C=1.0127) (90). Conversion to dihydrocodeinone, see page 252; to dihydrothebainone, page 317. —HYDROCHLORIDE, crystalline. —PICRATE, rods from alcohol, blacken at 230°, melt at 235° (89). —ACID CITRATE, cryst. from benzene-alcohol, decomp. 88° to 90° (90). —METHIODIDE, cryst. from alcohol, m. p. 257° (90). (Freund (89) finds needles from water, cont. $2H_2O$, m. p. 231°; from alcohol, it cryst. solvent-free, with the same melting

point, 231°.) —AMINE OXIDE, an oil, giving a Picrate as needles of m. p. 209° to 210° (89).

ACETYLODEMETHYLODIHYDROTHEBAINE (Acedicon) (94), experimental details of preparation not published. The base crystallizes from alcohol, m. p. 154° to 156°, insoluble in water, soluble in most organic media. Color reactions: nitric acid, yellow; conc. sulphuric acid, red; Fröhde's reagent, brown-red; Mandelin's reagent, red turning to dark brown; Mecke's reagent, red turning to dark brown; Marquis' reagent, red. The HYDROCHLORIDE m. p. 132° to 135° (decomp.) is easily sol. in water, and stable toward boiling water.

CYANONORDIHYDROTHEBAINE: $C_{19}H_{20}O_3N_2$, from the action of CNBr on dihydrothebaine, cryst. from acetic acid, m. p. 258° to 259° (89).

ISODIHYDROTHEBAIZONE: (85) $C_{19}H_{23}O_5N$, from ozonolysis of dihydrothebaine, cryst. of m. p. 103° to 105°, whose METHIODIDE m. 147° to 148° (decomp.). The base is exceedingly easily hydrolyzed to ISODIHYDROTHEBAIZONIC ACID, $C_{18}H_{21}O_5N$, cryst. from methanol, decomp. 248° to 249°, whose Hydrochloride decomp. at about 130°, Methiodide decomp. 179° to 180°. The acid hydrogenates to a Tetrahydroisothebaizonic acid of m. p. 230° to 235°.

DES-N-METHYLDIHYDROTHEBAINE (Dihydrothebainemethine): $C_{20}H_{25}O_3N$, from dihydrothebaine methiodide with alkali, cryst. from alcohol, m. p. 134° to 135°, whose METHIODIDE m. 243° (89), and gives as degradation product $C_{18}H_{18}O_3$, 6-methoxy-13-vinyltetrahydromorphenol methyl ether, m. p. 120° to 121°, which hydrolyzes with HCl to 6-keto-13-vinylhexahydromorphenol methyl ether, m. p. 149°. The latter hydrogenates to 6-keto-13-ethyloctahydromorphenol methyl ether, m. p. 113°, semicarbazone m. p. 191°. Aluminum amalgam in wet ether opens the ether linkage of the ketoethyloctahydromorphenol to yield 6-keto-13-ethyloctahydromorphol methyl ether, m. p. 148° to 150° (see below) (95). Des-N-methyldihydrothebaine hydrolyzes with hot 2 *N* HCl to give des-N-methyldihydrocodeinone (p. 252), or hydrogenates catalytically ($PdCl_2$) to give the oily DIHYDRO-DES-N-METHYLDIHYDROTHEBAINE, whose Hydrochloride is crystalline and whose Methiodide $C_{20}H_{27}O_3N \cdot CH_3I$ m. 217° to 222°. The last-named degrades to $C_{18}H_{20}O_3$, prisms of m. p. 119°, which hydrogenates to the 6-keto-13-ethyloctahydromorphol methyl ether, m. p. 148° to 150°, mentioned above. Dihydro-des-N-methyldihydrothebaine may be hydrolyzed to dihydro-des-N-methyldihydrocodeinone (p. 252) with hot dil. hydrochloric acid (96).

TETRAHYDROTHEBAINE (Dihydromorphine dimethyl ether, p. 159): $C_{19}H_{25}O_3N$, prep. by hydrogenation of thebaine hydrochloride in aqueous solution in the presence of palladium black; isolated as the picrate after separation of the other reduction products from the reaction mixture (91). A 60% yield of tetrahydrothebaine is said to be obtainable with a platinum oxide catalyst (92) (102). The base cryst. from ether or petroleum ether in large prisms of m. p. 83°, $[\alpha]_D^{18} = -152.7°$ (abs. alcohol, C=1.441). The HYDROCHLORIDE ($+3H_2O$) cryst. from acetone in needles, m. p. 115° to 116°, the PICRATE m. 222°. The METHIODIDE melts in its crystal-water at 135° to 140°, solidifies and remelts at 212° (91). CYANOTETRAHYDRONORTHEBAINE (100) cryst. from alcohol, melts at about 200°. The tetrahydrothebaines described by Oldenberg (88), Freund and Speyer (89), and Von Braun (72) were mixtures of reduction products.

DEHYDROTHEBAINE (80): $C_{19}H_{19}O_3N$, was obtained in very small yield from boiling thebaine with 30% hydrogen peroxide; yellow prisms from alcohol, m. p. 178° to 180°. The METHIODIDE cryst. from alcohol m. p. 177° (decomp.). PHENYLDIHYDROTHEBAINE, BENZYLDIHYDROTHEBAINE, see page 334. HYDROXYCODEINONE, from thebaine with hydrogen peroxide in acid solution (80) (81), see page 259.

α-THEBAIZONE: $C_{19}H_{21}O_5N$, prep. in 60% yield from the action of ozone on thebaine hydrochloride in aqueous solution (82) (83) (85); large pale yellow

crystals from ether or methyl alcohol, m. p. 125° to 126°. The base is easily saponified; with H_2SO_4 it gives red halochromism; it colors fuchsin-sulphurous acid in neutral or alkaline solution. —HYDROCHLORIDE, crystalline. —HYDRIODIDE, cryst. from acetone, m. p. 185° to 187°, browning at 178° (85). —SEMICARBAZONE, cryst. from ethyl acetate, m. p. 202° (corr.) (82). —METHIODIDE, $C_{19}H_{21}O_5N \cdot CH_3I$, cryst. from dil. methyl alcohol, decomp. 250° to 255°; it degrades to DES-N-METHYLTHEBAIZONIC ACID, isolated as the Hydrochloride, decomp. 260° to 270°; the Methiodide decomp. 250° to 255°, and can not be degraded further. BROMOTHEBAIZONE, $C_{19}H_{20}O_5NBr$, cryst. from methanol, m. p. 147° (85). THEBAIZONIC ACID, $C_{18}H_{19}O_5N$, from saponification of the methyl ester group of thebaizone with $Ba(OH)_2$; recryst. from ethyl acetate, decomp. about 235° (85). HYDROXYDIHYDROTHEBAIZONIC ACID, $C_{18}H_{21}O_6N$, from the action of warm conc. HCl on thebaizone, cryst. from dil. alcohol, decomp. 230° to 240°. Its Hydrochloride (from methanol) decomp. 205° to 210°, its Methiodide decomp. 163° and does not degrade. THEBAIZONE DICARBOXYLIC ACID, $C_{18}H_{19}O_6N + H_2O$, from thebaizone with 30% H_2O_2; yellow rods from water, m. p. 189° to 190° (decomp.) (85), 208° to 210° (86), whose Hydrochloride decomp. 242° (86). DIHYDROTHEBAIZONE, $C_{19}H_{23}O_5N$, from catalytic hydrogenation of thebaizone, m. p. unsharp 140°, soluble in water, phenolic in nature. Its Methiodide decomp. at 239° to 240°, Acetyl derivative methiodide decomp. 250°. DESOXYTHEBAIZONE, $C_{19}H_{21}O_4N$, from reduction of thebaizone with aluminum amalgam, yellow prisms from methyl alcohol, m. p. 147°, turning red. It reduces catalytically to DIHYDRODESOXYTHEBAIZONE, an oil, whose Methiodide cryst. from methyl alcohol, m. p. 175° to 177°, from water 148° to 152°, and degrades to DES-N-METHYLDIHYDRODESOXYTHEBAIZONIC ACID, decomp. 195° to 197°, whose Methiodide melting at 156° to 158° could not be further degraded. DIHYDRODESOXYTHEBAIZONIC ACID, $C_{18}H_{21}O_4N$ results from hydrolysis of dihydrodesoxythebaizone with hot HCl; m. p. 163° to 165° (decomp.); its Hydrochloride decomp. 236° to 237°.

β-THEBAIZONE: $C_{19}H_{21}O_5N$, is formed when α-thebaizone is heated for 2 minutes at 200°; yellow cryst. from methyl alcohol, m. p. 151°. HYDROXYDIHYDRO-β-THEBAIZONIC ACID, $C_{18}H_{21}O_6N \cdot H_2O$, from β-thebaizone with hot 2 *N* HCl, cryst. from dil. methanol, decomp. about 230°; the HYDROCHLORIDE decomp. 260°. β-THEBAIZONE (ESTER) CARBOXYLIC ACID, $C_{19}H_{21}O_6N$, from oxidation of β-thebaizone with 30% hydrogen peroxide; colorless cubes from methanol, decomp. ca. 220° (85).

THEBAOL (3, 6-dimethoxy-4-hydroxyphenanthrene): $C_{16}H_{14}O_3$, is formed when thebaine methiodide is heated with sodium methylate (65), or (as acetyl derivative) from thebaine or its methiodide with acetic anhydride (49) (50); cryst. from alcohol, m. p. 93° to 94°. ACETYLTHEBAOL, $C_{18}H_{16}O_4$, cryst. from alcohol, m. p. 118° to 122°; BROMOACETYLTHEBAOL, $C_{18}H_{14}O_4Br_2$, cryst. from acetic acid, m. p. 179°. ACETYLTHEBAOLQUINONE, $C_{18}H_{14}O_6$, from oxidation of acetylthebaol with CrO_3; yellow needles from acetic acid, m. p. 203°; with bromine it gives BROMOACETYLTHEBAOLQUINONE, m. p. 310°, with o-toluylenediamine it gives an Azine of m. p. 201° to 203°. Synthesis of acetylthebaolquinone, Pschorr (66). THEBAOLQUINONE, $C_{16}H_{12}O_5$, m. p. 233° (50), yields with o-toluylenediamine an Azine of m. p. 192°. METHYLTHEBAOL is an oil, giving a Picrate of m. p. 108° to 109°, a Dibromide of m. p. 123° to 124° (67) (68), and is identical with Pschorr's (66) synthetic 3,4,6-trihydroxyphenanthrene trimethyl ether. BENZOYLTHEBAOL, $C_{23}H_{18}O_4$, prep. from thebaine with benzoyl chloride at 0°, needles from dil. acetic acid, m. p. 160° to 161°. Its Dibromide m. 229°, and its Quinone m. 216° (69). THEBAOL DIMETHYLAMINOETHYL ETHER is an oil, giving a Picrate of m. p. 186°, and METHIODIDE of m. p. 199° to 200° (101).

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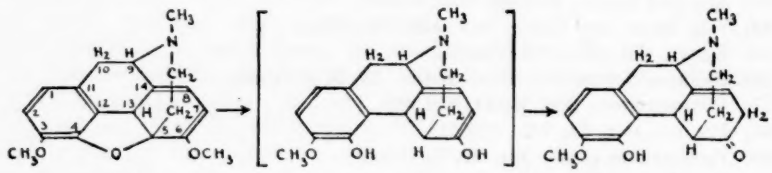
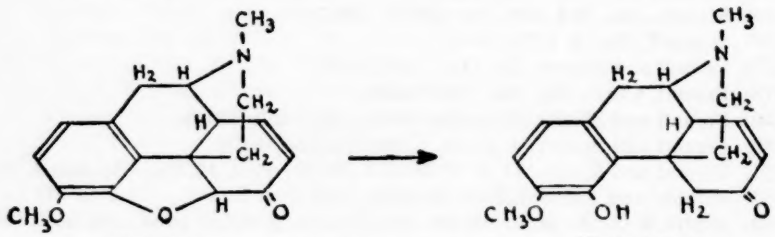
THEBAINONE

Thebainone is a ketonic compound derived from thebaine by hydrolysis of the enol ether group and simultaneous reductive scission of the 4, 5-ether bridge. This transformation was first accomplished by Pschorr (1) by the action of stannous chloride and concentrated hydrochloric acid on thebaine. Pschorr formulated the reaction in terms of his pyridine formula for thebaine. In the sense of the Knorr-Hörlein formula, later accepted by Pschorr, the reaction appears as:



Thebaine Thebainone

Thebainone is also related to codeinone, from which it may be prepared by heating with stannous chloride and hydrochloric acid (2).

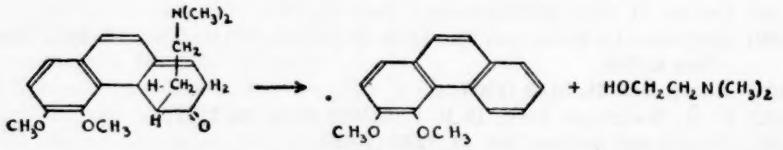


Codeinone Thebainone

(Gulland-Robinson Formulation)

Of the three oxygen atoms originally present in thebaine, one is shown by the methoxyl determination to be still in a CH_3O group; the second is phenolic (formation of a sodium salt and a methyl ether) and the third gives the reactions of a ketone oxygen. The positions of the oxygens follow from the relationship to codeinone and the degradation to 3, 4-dimethoxyphenanthrene. The results of exhaustive methylation show that nitrogen is tertiary and in a ring.

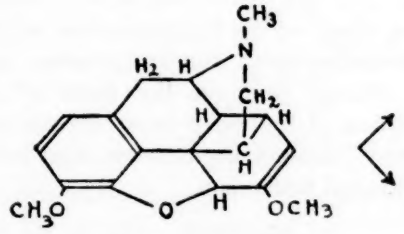
When methylthebainonemethine is heated with acetic anhydride, ethanoldimethylamine and dimethylmorphol result (4), a decomposition parallel to that of the methylmorphimethines (p. 270).



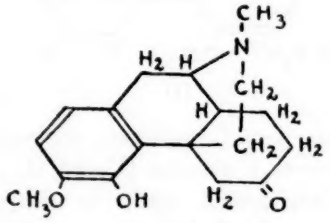
On the basis of the now abandoned oxazine structure for the morphine alkaloids, ethanoldimethylamine was believed to be formed through

hydrolysis of an etherlike linkage of the $-CH_2-CH_2-N-CH_3$ chain with the nucleus. The degradation of methylthebainonemethine (4), in which the function of every oxygen atom was known, showed that the formation of ethanoldimethylamine could take place when a carbon-to-carbon bond broke (4); the oxazine hypothesis (see p. 337) lost thereby one of its strongest supporting arguments.

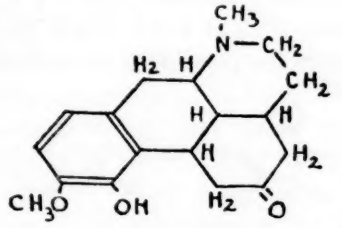
When thebainone is reduced with sodium amalgam (1), a compound containing two more hydrogen atoms is obtained. Pschorr, considering this to have been formed by reduction of the ketone to a secondary alcohol, named it thebainol. In a repetition of Pschorr's experiment, Gulland and Robinson (5) (1923) found that thebainol is actually a ketone, and hence must have been formed by saturation of the double linkage in thebainone. Thebainol should logically be named dihydrothebainone; this name, however, is already claimed by an isomeric substance, prepared by catalytic hydrogenation of thebaine (6) (7). (*Cf.* Wieland and Kotake (10).) Dihydrothebainone is a tertiary, basic, phenolic ketone, which has the phenolic hydroxyl on C-4, and the keto group at C-6. To explain the isomerism with thebainol, Gulland and Robinson suggested that the bridge system which they at that time postulated as present in thebaine must have broken in each of the two conceivable directions. (*Cf.* Freund's explanation of the supposed formation of two tetrahydrodesoxycodeines, p. 240.)



Thebaine (Gulland-Robinson, 1923)



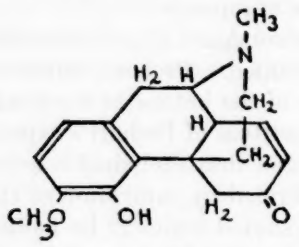
Thebainol



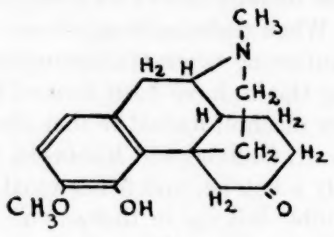
Dihydrothebainone

In a revision of their thebaine formula, the same investigators (8) mention the possibility of a stereochemical explanation of the isomerism.

New light has been thrown on the nature of the thebainol-dihydrothebainone isomerism by the investigations of Schöpf (3) (12). The most obvious structure for thebainone is that represented by I below; it is however excluded, for the reduction product (II) of thebainone, namely thebainol, would be identical with dihydrothebainone.

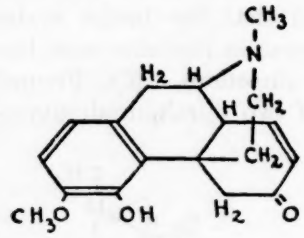


I

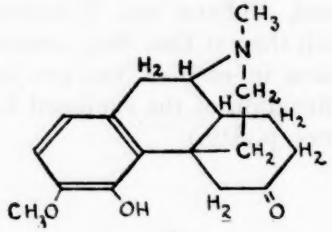


II

Another possibility is that a change in configuration on C-14 has taken place during thebainone formation, in which case thebainone and its reduction product would be depicted by III and IV.

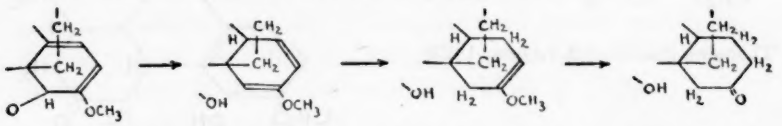


III



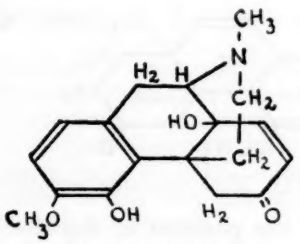
IV

This would represent thebainol and dihydrothebainone as stereoisomers, Formulas IV and II. A study of the hydrogenation of thebaine, which leads to dihydrothebainone, dihydrothebaine, and tetrahydrothebaine, convinced Schöpf that on the basis of the Robinson thebaine formula addition of hydrogen must always take place first at C-14, which thereby becomes asymmetric, and introduces the possibility of configurational isomerism:



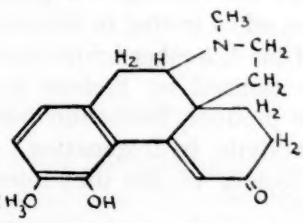
It was in fact possible to isolate (as oxime) from the hydrogenation of thebaine with palladium on calcium carbonate a stereoisomer of dihydrothebainone, dihydro-epi-thebainone. This excludes Formula IV for thebainol, hence III can not represent thebainone (3).

The assumption of a double bond between C-7 and C-8 in thebainone is without support. Were it in this position, thebainone should closely resemble hydroxythebainone, V



V. Hydroxythebainone

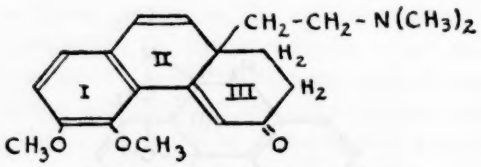
whose formula is established by its hydrogenation (17) to dihydrohydroxythebainone. (See p. 316.) In marked contrast to thebainone, hydroxythebainone shows no halochromism in concentrated hydrochloric acid. The only explanation of the deep orange-red halochromism of thebainone lies in a conjugation of the double bond with the carbonyl group and the aromatic ring, i. e., it must occupy the 5, 13-position. Only on this assumption can the great similarity (12) of thebainone to salicylideneacetone and salicylideneacetophenone be explained. From this, it follows that the ethanamine chain can not be attached as in thebaine to C-13, but must have been shifted to another point; on the grounds given below, Schöpf believes that it is linked to C-14, and proposes that the compound be given the name metathebainone.[3] The old nomenclature will be retained in this discussion. The Schöpf mechanism for the codeinone-thebainone transformation is depicted on page 330.



VI. Metathebainone (Schöpf (3) 1927)

The side chain can not occupy position 8, as in morphothebaine, for then the morphol scission of methylthebainonemethine (VII) would be inexplicable on the basis of the Robinson theory that loss of the side chain takes place only when necessary to permit Ring III to become aromatic; the ethanamine chain must be on a quaternary carbon atom, i. e., on C-14. Furthermore, if the side chain is in any position except 14, the methine bases of the thebainone series should undergo with great ease a shift of the double bond in such a way (to C-13-C-14) as to make Ring II aromatic.

[3] The preparation of the true thebainone of the structure represented in formula I has been announced in a preliminary communication (Schöpf and Perrey, Ann. 483, 170 (1930)). See Appendix, p. 336.

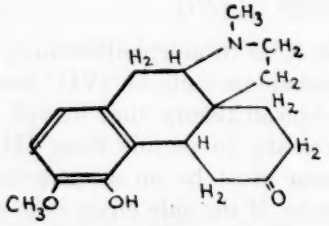


VII. Methylthebainonemethine

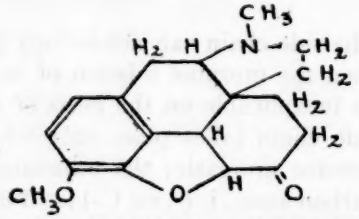
Schöpf believes that the position of the double bond at C-5-C-13 accounts for the extreme difficulty of hydrogenating thebainone. Methylthebainone is unaffected by ozone, a fact which Wieland and Small (14) find difficult of explanation on the basis of the Schöpf formula.

Thebainol must be formed by the saturation of the C-5-C-13 double bond, whereby an asymmetric carbon atom is generated; it would be a direct proof of the correctness of the Schöpf thebainone formula if the existence of stereoisomeric reduction products of thebainone could be shown. Hoek (13) believed to have isolated such an isomer, but attempts to duplicate his results have failed (3). Ochiai and Kondo (24) (31) describe the preparation of β-dihydrothebainone by catalytic reduction of thebainone, but ignore its significance for the Schöpf formula; whether it is the predicted stereoisomer of thebainol remains to be settled.

Thebainol (Schöpf nomenclature "dihydrometathebainone") reacts with two molecules of bromine, replacing one hydrogen atom of the aromatic nucleus, and one hydrogen atom at C-5 with bromine. This dibromo product, when heated in alkali, eliminates the bromine at C-5 with closure of the 4, 5-ether bridge (compare the re-formation of the ether linkage claimed by Pschorr in the β-ethylthiocodide series, p. 231). The product, bromodihydrometacodeinone, can be debrominated by catalytic hydrogenation, yielding dihydrometacodeinone (26), an isomer of the dihydrocodeinone described on page 249



VIII. Thebainol (Dihydrometathebainone)



IX. Dihydrometacodeinone

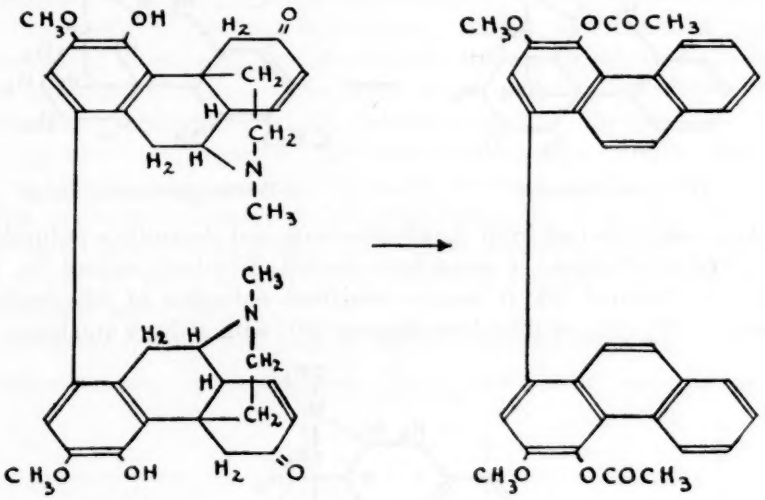
Dihydrometacodeinone is reduced back to dihydrometathebainone by treatment with sodium amalgam in alcohol. It rearranges to thebainone (metathebainone) with great ease in the presence of acid or alkali, or during oxime formation.

Thebainone adds hydroxylamine in a manner typical of α,β-unsaturated ketones (3).

The nitrogen ring of thebainone is stable toward boiling acetic anhydride (21).

An asymmetric carbon atom of thebainone is inverted by the action of silver nitrate, resulting in the formation of a stereoisomer, pseudothebainone. This may be hydrogenated to dihydropseudothebainone, a fifth dihydrothebainone (29) (31). Pseudothebainone differs from the dithebainone described below, which is obtained by a similar method (Ann. **481**, 87 note 1 (1930)).

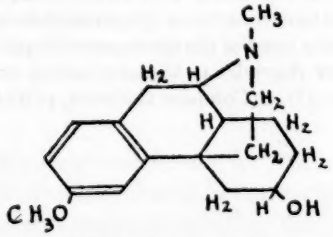
Oxidation of thebainone with silver nitrate by the Goto [4] method results in a dimolecular product, dithebainone, to which Goto and Kitasato (32) assign the structure below. By acetolysis, its methine base yields a nitrogen-free product, bis(1, 1′)-3-methyl-4-acetylmorphol:



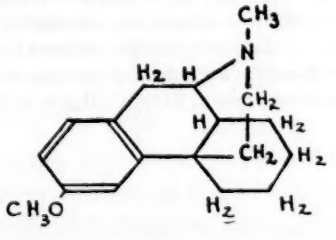
Dithebainone

Dithebainone occurs in two forms, designated as α- and β-; the nature of the isomerism is not known.

Dihydrothebainone (from thebaine reduction) reduces by the electrolytic method to an alkali-insoluble substance, dihydrothebacodine (9); the phenolic hydroxyl is believed to be replaced by hydrogen, and the keto group reduced to a secondary alcohol. This alcoholic group reacts with phosphorous pentachloride, yielding chlorodihydrothebacodide; the chlorine of chlorodihydrothebacodide can be reductively eliminated, with formation of desoxydihydrothebacodine.



Dihydrothebacodine

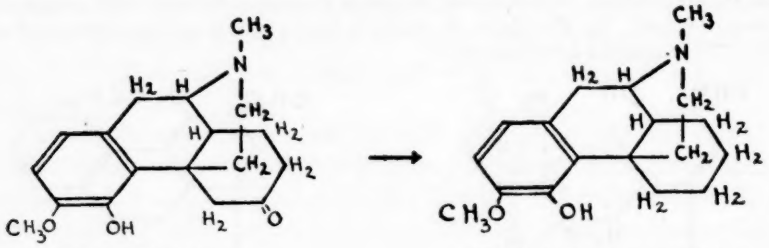


Desoxydihydrothebacodine

[4] J. Chem. Soc. Japan (Nippon Kwagaku Kwai Shi) **50**, 603 (1929).

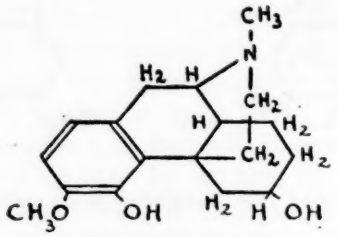
Clemmensen reduction of dihydrocodeinone or dihydrothebainone likewise yields dihydrothebacodine (25) (30).

Desoxytetrahydrosinomenine, derived from the alkaloid sinomenine, proved to be the optical antipode of dihydrothebacodine (25). Since Kondo and Ochiai (28) showed desoxytetrahydrosinomenine to have a phenolic hydroxyl at C-4, they conclude that the Speyer formula for dihydrothebacodine must be incorrect, and that it still contains the phenolic hydroxyl. Direct comparison with β-tetrahydrodesoxycodeine showed it to be identical with this substance (30) (34).



Dihydrothebainone β-Tetrahydrodesoxycodeine

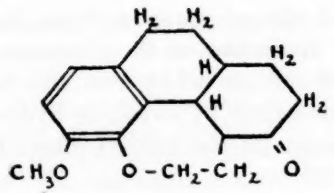
As a minor product from the above-mentioned electrolytic reduction of dihydrothebainone, a secondary alcohol, dihydrothebainol (m. p. 142°) is obtained (9); it results also from reduction of dihydrothebainone (25) (31), or dihydrocodeinone (30) with sodium amalgam.



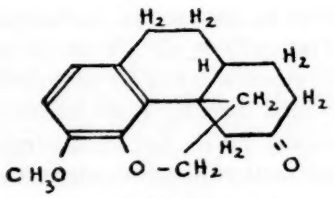
Dihydrothebainol

Another dihydrothebainol (m. p. 165°) is formed when dihydrothebainone is hydrogenated in the presence of platinum; it is likewise a phenol and an alcohol (7). It is not known if the new asymmetric carbon atom at C-6 is responsible for the isomerism.

Exhaustive methylation of dihydrothebainone proceeds with the formation of a methine base, des-N-methyldihydrothebainone (6), which is likewise obtained by reduction (aluminum amalgam) of the methine base from dihydrocodeinone (11). Catalytic hydrogen reduces the 9, 10-double bond of the des-base to dihydrodes-N-methyldihydrothebainone, which further degrades to trimethylamine and thebenone (see p. 318), $C_{17}H_{20}O_3$, a cyclic ether (11). (Compare thebenol, p. 324.)



I. Thebenone

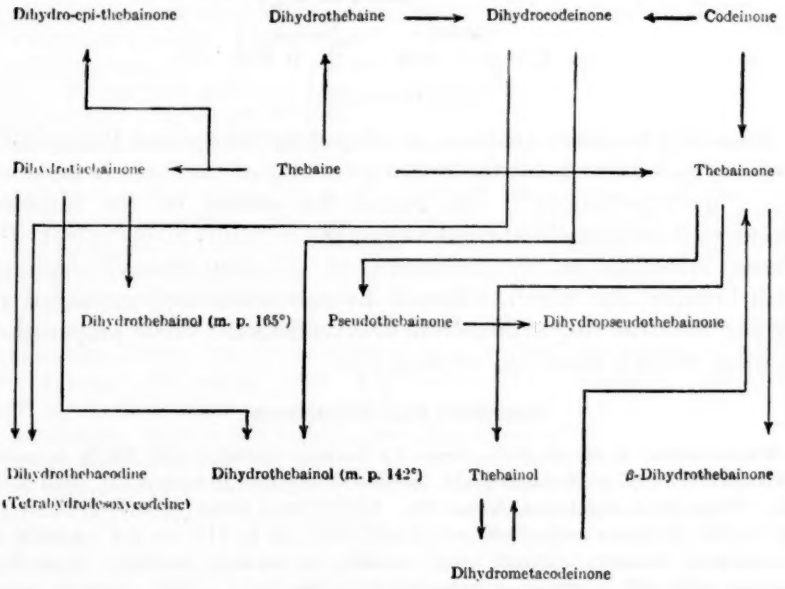


II. Thebenone

Thebenone condenses only once with reagents for the active $-CH_2-$ group (11); this does not necessarily exclude Formula II from consideration (12).

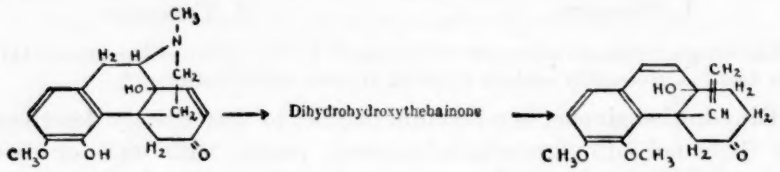
Dihydrothebainone, in a reaction parallel to that already described for thebainol (dihydrometathebainone), reacts with one or two molecules of bromine to give respectively 1-bromodihydrothebainone or a dibromothebainone. The latter is converted by alkali into 1-bromodihydrocodeinone, which debrominates to dihydrocodeinone (see p. 250), an isomer of the dihydrometacodeinone mentioned above. Bromodihydrocodeinone, in which the 4, 5-ether linkage is closed, is changed back to the phenolic bromodihydrothebainone by reduction with zinc and alcohol (35). The ether ring closure through the action of bromine and alkali has been carried over into the Sinomenine series (35).

The above relationships may be summarized as follows:



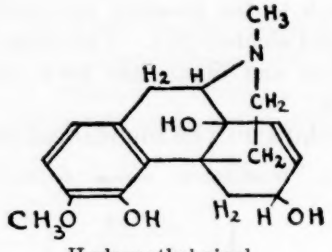
Hydroxycodeinone (p. 254), when treated with stannous chloride in hydrochloric acid, is converted to hydroxythebainone (16) (17) (19), a transformation recalling that of codeinone to thebainone, but apparently not involving the shift of the ethanamine chain assumed by

Schöpf in the case of thebainone. The hydroxyl group occupies the 7- (16) (17) or the 14- (3) (8) position. Reduction of the compound catalytically leads to dihydrohydroxythebainone which can also be obtained directly from hydroxycodeinone oxime by catalytic hydrogenation (16). On exhaustive methylation (of the methyl ether) it gives methyldihydrohydroxythebaone (12).



Hydroxythebainone — Methyldihydrohydroxythebaone

Reduction of hydroxycodeinone with zinc in formic acid yields hydroxythebainol, by reduction of the ether bridge and the keto group.



Hydroxythebainol

According to recent evidence developed by Schöpf and Perrey (35) hydroxythebainone is not the hydroxy- analog of the Pschorr thebainone ("metathebainone") but rather the analog of the hitherto unknown thebainone in which the ethanamine chain still occupies C-13. These investigators, by treatment of dihydrohydroxythebainone with bromine and alkali, followed by debromination, succeeded in closing the ether ring to dihydrohydroxycodeinone, whose preparation in other ways is described on page 256.

Descriptive Part (Thebainone)

THEBAINONE: B=$C_{18}H_{21}O_3N$, Prep. by heating thebaine with $SnCl_2$ in conc. HCl at 100° for 15 to 20 minutes (1); modified procedure Robinson (5), yield 53% (3). Prep. from codeinone, Knorr (2). Cryst. from water, B+1½ H_2O, m. p. 88° to 90° (3), from methyl alcohol, B+CH_3OH, m. p. 115° to 118°; soluble in chloroform, benzene, acetone, ethyl acetate, or alcohol, sparingly in methyl alcohol, with diff. in ether, or water (cold 1 : 250, hot 1 : 120). SODIUM SALT, orange plates. —PICRATE, m. p. 250° to 253° (corr.). —METHIODIDE, m. p. 255° to 256° (corr.). With alkali it degrades to DES-N-METHYLTHEBAINONE, yellow needles from methanol, m. p. 170° to 171°, whose Methiodide (cryst. from acetone) melts at 252° and does not degrade with NaOH. Des-N-methylthebainone oxime, cryst. from alcohol, m. p. 210° to 211° (3). Reduction of des-N-methylthebainone catalytically gives DIHYDRO-DES-N-METHYLTHEBAINONE,

whose HI melts at 258° to 259°. When reduction is accomplished with sodium amalgam, des-N-methylthebainol (see below) is formed. THEBAINONE OXIME ($+CH_3OH$) m. p. 200° to 201° (corr.). —SEMICARBAZONE, m. p. 227° (corr.). —PHENYLHYDRAZONE, not cryst. —METHYL ETHER (from action of diazomethane) m. p. 156° (corr.), gives a Methiodide of m. p. 256° (corr.), $[\alpha]_D^7 = +182.48°$ (23), whose methine, DES-N-METHYLMETHYLTHEBAINONE, m. at 65° to 66°: –Semicarbazone ($+C_2H_5OH$) m. 107° to 108° (corr.); –Oxime hydrochloride, m. p. 271° to 272° (corr.). The Methine methiodide ($+C_2H_5OH$) melts at 171° to 172°. By reduction of des-N-methylmethylthebainone with sodium amalgam in alcohol, the oily Des-N-methylmethylthebainol is obtained, whose Perchlorate melts 193° to 194°. Further reduction (catalytic) gives Dihydro-des-N-methylmethylthebainol (see under thebainol) (3). Reduction of the des-N-methylmethylthebainone, catalytically, gives Dihydro-des-N-methylmethylthebainone, whose Methiodide m. 154° to 155°. This new base reduces with sodium amalgam to Dihydro-des-N-methylmethylthebainol (3), (see below). ACETYLTHEBAINONE (cryst. from ether-pet. ether) m. p. 100° to 101°, is easily saponified; it gives a Methiodide, m. p. 223° to 225° (corr.), a Semicarbazone, m. p. 249° (corr.) and Phenylhydrazone, m. p. 225° to 226° (corr.) (1). BENZYLIDENETHEBAINONE (5) (22) yellow needles from alcohol, m. p. 233°; sol. in benzol, chloroform, crimson solution in dil. alkali; green color with alcoholic $FeCl_3$. The Picrate decomp. 194°, Methiodide, m. p. 195° to 197°. Benzylidenethebainone reduces catalytically to give isomeric benzylthebainones; BENZYLTHEBAINONE-A, colorless needles from alcohol, m. p. 229°, orange Sodium salt, Semicarbazone m. p. 155° to 160°. BENZYLTHEBAINONE-B, plates from alcohol, m. p. 179°, Semicarbazone, m. p. 140° to 145°, Oxime colorless columns from alcohol m. p. 152° (22). PIPERONYLIDENETHEBAINONE (5) (22) cryst. from alcohol, m. p. 176°. DIANHYDRO-6-AMINOPIPERONALTHEBAINONE DIHYDROBROMIDE ($+3H_2O$) m. p. 258° to 260.°

PSEUDOTHEBAINONE: $C_{18}H_{21}O_3N$, from treatment of thebainone with $AgNO_3$; needles, decomp. 277°, $[\alpha]_D^{16} = -339.5°$; the SEMICARBAZONE is not decomp. at 290°. By catalytic reduction, DIHYDROPSEUDOTHEBAINONE is obtained, needles decomp. 270°, $[\alpha]_D^{25} = -71.77°$ (29).

α-DITHEBAINONE (32): $(C_{18}H_{20}O_3N)_2$, prep. by oxidation of thebainone with silver nitrate or potassium ferricyanide; colorless needles from ethyl alcohol, m. p. 308° to 310° (decomp.); $[\alpha]_D^{23} = -532.6°$ (chloroform, C=2.283). The DIACETYL DERIVATIVE m. 272° to 273°, $[\alpha]_D^{20} = -321.4°$ (benzene, C=1.512). α-DITHEBAINONE METHIODIDE, colorless crystalline powder decomp. 274°. TETRAHYDRO-α-DITHEBAINONE, $(C_{18}H_{22}O_3N)_2$ prisms from methanol, decomp. above 300°; $[\alpha]_D^{23} = -390.6°$ (alcohol; C=1.5924).

β-DITHEBAINONE: $(C_{18}H_{20}O_3N)_2$, obtained from the mother liquors from preparation of the α-form. M. p. 235° to 237°, $[\alpha]_D^7 = -327.9°$ (chloroform, C=1.107). The METHIODIDE decomp. 274°. TETRAHYDRO-β-DITHEBAINONE $(C_{18}H_{22}O_3N)_2 + 3CH_3OH$, m. p. 266°, $[\alpha]_D^{24} = -223.9°$ (chloroform, C=1.6712). Both α- and β-dithebainone degrade to the same dimorphenol derivative.

DIHYDROTHEBAINONE: $B = C_{18}H_{23}O_3N$, from reduction of thebaine in acetic acid with hydrogen and palladium; cryst. from alcohol, m. p. 137° to 138°, $[\alpha]_D^{20} = -80.12°$ (alcohol, C=0.8424) (7) (*cf.* Freund and Speyer (6) (20)). Schöpf (15) found the m. p. 138° to 143°, decomp. 148°; $[\alpha]_D^{18} = -72.5°$ (abs. alcohol, C=1.048), $[\alpha]_D^{18} = -74.5°$ (benzene, C=0.490). The base is soluble in alkali and precip. out of alkaline solution with NH_4Cl. Dihydrothebainone has also been prep. by reduction of dihydrothebaine, catalytically, or with sodium in amyl alcohol (6). —HYDROCHLORIDE (6), crystalline, $[\alpha]_D^{20} = -50.71°$ (water, C=2.465). —HYDRIODIDE (6)[5] decomp. 262° to 263°. —METHIODIDE, m. p. 116°

[5] The purity of these compounds has been questioned; see Skita (7).

(7), (150° (6)). —OXIME, m. p. 250° (7), (253° to 255° (6)), $[\alpha]_D^{20} = +6.6°$ (10% acetic acid, C=0.533) (3). The Oxime hydrochloride m. at 318° (6), (305° (15)). —SEMICARBAZONE, m. p. 226° to 227° (5), (237° (33)). PIPERONYLIDENE DIHYDROTHEBAINONE, yellow prisms, m. p. 174° to 175° (11). BENZYLIDENE DIHYDROTHEBAINONE, pyramids from alcohol, m. p. 188° (22). DIHYDROTHEBAINONE METHYL ETHER is not crystalline, but yields a cryst. Methiodide of decomp. pt. 257° to 258°; by degradation of this methiodide DES-N-METHYLMETHYLDIHYDROTHEBAINONE (methyldihydrothebainonemethine) is obtained, cryst. from ligroin m. at 89.5°, whose Hydriodide m. 211° to 212°, Semicarbazone m. 184°, and Methiodide m. 189°; degradation of the last named failed. Des-N-methylmethyldihydrothebainone hydrogenates to DIHYDRO-DES-N-METHYLMETHYLDIHYDROTHEBAINONE, cryst. from ligroin, m. p. 70.5° to 72°, whose Hydriodide m. 224° to 225°, Perchlorate m. 216°, Semicarbazone m. 176° to 178°, and Methoperchlorate m. 185° to 186° (27).

1-BROMODIHYDROTHEBAINONE (35): $C_{18}H_{22}O_3NBr + \frac{1}{2}C_4H_8O_2$, prep. by bromination of dihydrothebainone in gl. acetic acid, isolated as the hydriodide. The base cryst. from ethyl acetate, and holds ½ molecule of solvent; it m. solvent-free at 167°. —HYDROBROMIDE, foams at 100° to 112°, melts again at 210° to 215°. —OXIME, sinters 168°, m. at 178° to 180° (foaming).

DES-N-METHYLDIHYDROTHEBAINONE: $C_{19}H_{25}O_3N$ (dihydrothebainonemethine), from heating dihydrothebainone methiodide with alkali; m. p. 183°, $[\alpha]_D^{20} = +60.7°$ (dil. acetic acid, C=0.454). —HYDRIODIDE, m. p. 170° to 180° (6). The same des-base was obtained by Wieland and Kotake (11) from reduction of des-N-methyldihydrocodeinone with amalgamated aluminum in moist ether. It hydrogenates further to DIHYDRO-DES-N-METHYLDIHYDROTHEBAINONE, m. p. 154° to 156°, (Picrate, m. p. 185° to 188° (11), Perchlorate, m. p. 233° (27), Methiodide, m. p. 226° to 229°, Picrate of Acetyl derivative, m. p. 188° to 192°, Piperonylidene derivative, m. p. 179° to 181° (11)). Dihydro-des-N-methyldihydrothebainone methiodide degrades to THEBENONE, m. p. 134° to 136°, whose Oxime m. 201° to 204°, Isonitroso compound m. 165°, Benzal derivative m. p. 162°, Piperonal derivative m. 185° to 186° (11) (12). (*Cf.* Cahn (27).) Thebenone oxidizes with chromic acid to a diketone $C_{17}H_{18}O_4$, m. p. 185° to 187° whose Dioxime melts at 155° to 160°, solidifies, and remelts at 260°. Dihydro-des-N-methyldihydrothebainone is most easily prepared by catalytic hydrogenation of des-N-methyldihydrothebaine (11).

β-DIHYDROTHEBAINONE (24): $C_{18}H_{23}O_3N$, from reduction of thebainone with hydrogen and palladium, white needles sintering at 62° to 64°, m. p. 76°, $[\alpha]_D^{27} = -83.94°$. The Picrate decomp. 245°, the SEMICARBAZONE decomp. 199° to 201°.

DIHYDRO-EPI-THEBAINONE, Oxime, m. p. 228° (3) (15), $[\alpha]_D^{20} = -115.8°$ (10% acetic acid, C=0.552).

THEBAINOL (1): B=$C_{18}H_{23}O_3N$, from reduction of thebainone with sodium amalgam in dilute alkali; cryst. from CH_3OH, m. p. 54° to 55°, solidifying and m. again at 76° to 78°; from dry ether, m. p. 135° to 136° (5), rectangular prisms; $[\alpha]_D^{25} = +67.05°$ (alcohol, C=8.71), $[\alpha]_D^{25} = +33.07°$ (5% acetic acid, C=2.368). The PERCHLORATE, cryst. from alcohol, m. p. 245°, may be used to purify the base (3). —SEMICARBAZONE (from dil. alcohol) m. p. 217° to 218°. —OXIME, from alcohol, m. p. 217° to 218°, $[\alpha]_D^{18} = +104.2°$ (10% acetic acid, C=0.518). —METHIODIDE, decomp. 243°, $[\alpha]_D^{25} = +46.56°$ (water, C=2.061). BENZYLIDENETHEBAINOL, yellow needles, m. p. 100° to 102° (22). DIPIPERONYLIDENE DERIVATIVE, ($+2H_2O$) orange-yellow non-cryst. powder (5). THEBAINOL METHYL ETHER is non-cryst. but gives a Methiodide, decomp. 245°, (260° (3)) and a Piperonylidene comp., non-cryst. m. about 156° (5). The methiodide degrades to an oily des-base, which hydrogenates. The product was isolated as

DIHYDRO-DES-N-METHYLMETHYLTHEBAINOL METHIODIDE, m. p. 117° to 118°, or METHYL PERCHLORATE, m. p. 215°, $[\alpha]_D^{18} = -44.9°$ (acetone, C=0.504) (3).

DES-N-METHYLTHEBAINOL is obtained by reduction of des-N-methylthebainone with sodium amalgam in dilute alkali. Cryst. from alcohol, m. p. 173° to 174°. It reduces catalytically to DIHYDRO-DES-N-METHYLTHEBAINOL of m. p. 119° to 121°, whose Methyl ether obtained in a different way is described above (3).

DIHYDROTHEBAINOL: B=$C_{18}H_{23}O_3N$, in small yield from electrolytic reduction of dihydrothebainone; cryst. with ½ H_2O, decomp. 138° to 142°, $[\alpha]_D^{28} = -46.2°$ (alcohol, C=0.789). It is obtained in better yield by reduction of dihydrothebainone with sodium amalgam (31). —HYDROCHLORIDE, decomp. 268°. —HYDRIODIDE, B·HI. —METHIODIDE, m. p. 280° (from dil. alcohol), $[\alpha]_D^{29} = -24.25°$ (methanol, C=0.907) (25). —METHYL ETHER, m. p. 181° to 182°, giving a Methiodide of m. p. 284° to 285°. Dihydrothebainol methiodide degrades to the oily Des-N-methyldihydrothebainol, whose Hydriodide m. 179° to 180° and Methiodide m. 281° to 282°; further degradation of the latter gave trimethylamine and an oily product (9). A second DIHYDROTHEBAINOL was obtained by catalytic reduction of dihydrothebainone: needles m. p. 165°, $[\alpha]_D^{20} = -36.5°$ (alcohol, C=0.905). —METHIODIDE, m. p. 273° (from alc.). —BIS-PHENYLURETHANE, m. p. 175° (7).

HYDROXYTHEBAINONE: (16) (17) (19) B=$C_{18}H_{21}O_4N$, from hydroxycodeinone with $SnCl_2$ and HCl at 100°, cryst. from alc.-ether, decomp. 104° to 106°. —HYDROCHLORIDE, decomp. 305°, $[\alpha]_D^{18} = -68.65°$ (water, C=1.6024). —OXIME, decomp. 255°. HYDROXYTHEBAINONE DIBROMIDE, decomp. 258°, reduces with catalytic hydrogen to DIHYDROHYDROXYTHEBAINONE (17). HYDROXYTHEBAINONE METHIODIDE, m. p. 245°. ACETYL HYDROXYTHEBAINONE, m. p. 197° (from alc.), giving an Oxime m. 216° to 218° and a Methiodide decomp. 212° to 213°.

DIHYDROHYDROXYTHEBAINONE (16) (17) (18): B=$C_{18}H_{23}O_4N$, from catalytic reduction of hydroxythebainone or its dibromo compound, or by electrolytic, or sodium- zinc- or aluminum-amalgam reduction of dihydrohydroxycodeinone. Recryst. from ligroin, m. p. 140° to 145°. —HYDROCHLORIDE, decomp. 310°, $[\alpha]_D^{20} = -52.47°$ (water, C=2.443). —PERCHLORATE, m. p. 170° to 180° (from water), decomp. 270° (from alcohol). —OXIME, 220° to 222°. —METHIODIDE, (+H_2O) decomp. 210°, which degrades to DES-N-METHYLDIHYDROHYDROXYTHEBAINONE of m. p. 242° to 243°, $[\alpha]_D^{20} = -81.88°$ (dil. acetic acid, C=2.498) whose Hydriodide m. ca. 158°. The des-base reduces to a tetrahydro base, DIHYDRO-DES-N-METHYLDIHYDROHYDROXYTHEBAINONE, of m. p. 239° to 240°, $[\alpha]_D^{20} = -45.25°$ (dil. acetic acid, C=1.316), whose cryst. Methiodide degrades to TETRAHYDROHYDROXYTHEBAONE, m. p. 143° to 144°. ACETYLDIHYDROHYDROXYTHEBAINONE, m. p. 214° (from alc.). DIHYDROHYDROXYTHEBAINONE METHYL ETHER (18), m. p. 151° to 153°, giving a Perchlorate (+H_2O) m. p. 134° and a Methiodide m. 206° to 208°; the Methiodide splits to DES-N-METHYLMETHYLDIHYDROHYDROXYTHEBAINONE, m. p. 131° to 133°, whose CH_3I m. 209° and degrades to METHYLDIHYDROHYDROXYTHEBAONE, m. p. 87° to 89°, $C_{18}H_2O_4$. The des-base above of m. p. 131° to 133° reduces to $C_{20}H_{29}O_4N$, DIHYDRO-DES-N-METHYLMETHYLDIHYDROHYDROXYTHEBAINONE, m. p. 83° to 85°, whose Methiodide degrades to METHYLTETRAHYDROHYDROXYTHEBAONE, m. p. 74° to 76°, which is also obtained when methyldihydrohydroxythebaone is reduced.

HYDROXYTHEBAINOL (17): B=$C_{18}H_{23}O_4N$, from reduction of hydroxycodeinone, electrolytic or Zn-Cu in 85% formic acid; prisms from $CHCl_3$, m. p. 234°; does not react with ketone reagents. —HYDROCHLORIDE, crystalline. —HYDROBROMIDE, m. p. 252° to 253°. —HYDRIODIDE (+H_2O) m. p. 247° (from water). —PICRATE, m. p. 204° to 205°. FORMYLHYDROXYTHEBAINOL, m. p. 277°, whose HI decomp. 305°+. BENZOYLHYDROXYTHEBAINOL, decomp. 257°. HYDROXYTHEBAINOL-N-OXIDE, decomp. 237°. HYDROXYTHEBAINOL METHYL ETHER was

obtained as the Methiodide ($+H_2O$), decomp. 233°; it degrades to DES-N-METHYLHYDROXYTHEBAINOL METHYL ETHER m. at 195° to 197°, whose HI m. 255° and CH_3I decomp. 239° to 240°, $[\alpha]_D^{20} = +141.8°$ (water, C=1.279). The last-mentioned degrades to $C_{18}H_{20}O_4$, m. p. 188° to 189°, $[\alpha]_D^{19} = -29.01°$ ($CHCl_3$, C= 1.614). BROMOHYDROXYTHEBAINONE, m. p. 230° to 231°.

DIHYDROTHEBACODINE (9): $C_{18}H_{25}O_2N + \frac{1}{2}H_2O$, prep. by electrol. reduction of dihydrothebainone in dil. H_2SO_4, Tafel method. Cryst. from dil. alcohol, m. p. 149°. The HYDRIODIDE cryst. from water in needles, m. p. 151° to 152° (*cf.* Kondo and Ochiai (31) m. p. 250° to 251°). The METHIODIDE, scales from water. By degradation of the methiodide, DES-N-METHYLDIHYDROTHEBACODINE is obtained, needles from alcohol containing a little water, m. p. 147° to 150°, whose Methiodide, oily, degraded to the nitrogen-free compound $C_{17}H_{20}O_2$, needles from dil. acetic acid, m. p. 109° to 110°. Dihydrothebacodine is probably identical with β-tetrahydrodesoxycodeine (30) (34).

CHLORODIHYDROTHEBACODIDE (9): $C_{18}H_{24}ONCl$, from treatment of dihydrothebacodine with PCl_5; columns from alcohol, sinter 125°, m. p. 132°, giving a METHIODIDE which cryst. from water m. p. 240° to 241° (decomp.).

DESOXYDIHYDROTHEBACODINE (9): $C_{18}H_{25}ON$, from reduction of chlorodihydrothebacodide with sodium in alcohol; yellow leaflets from alcohol cont. a little water, sinter 137° to 138°, m. 146°. Its HYDRIODIDE, columns from water, sinters 250°, decomp. 252°. The METHIODIDE cryst. from water in rhombic columns, sinter 264°, m. 266° to 267°. By its degradation is obtained DES-N-METHYLDESOXYDIHYDROTHEBACODINE, $C_{19}H_{27}ON + C_2H_5OH$, cryst. from dil. alcohol, m. p. 132° to 133°, whose Methiodide m. 261° to 262° and degrades to $C_{17}H_{20}O$, m. p. 98° to 99°.

DIHYDROHYDROXYTHEBACODINE (30): $C_{18}H_{25}O_3N$, see under Dihydrohydroxycodeinone, page 260.

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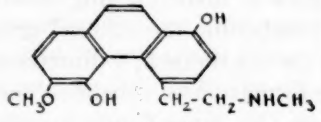
THEBENINE

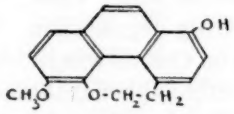
Thebenine, $C_{18}H_{19}O_3N$, is a secondary amine which results from the action of hot dilute hydrochloric acid on thebaine (1) or codeinone (2). It is also formed as the triacetyl derivative when pseudocodeinone is treated with acetic anhydride (3). If hydrochloric acid in methyl alcohol solution is allowed to act on thebaine at 100°, thebenine monomethyl ether is formed, the so-called methebenine, and in ethyl or propyl alcohol solution the corresponding ethers, ethebenine and prothebenine, are obtained (4).*

On degradation by the Hofmann method, thebenine splits into trimethylamine and a nitrogen-free portion, thebenol, which contains a phenolic hydroxyl, a methoxyl group, and an indifferent oxygen linked in an ether ring. When ethyl iodide is used for the degradation, the basic product is methyldiethylamine (5), whence it is certain that the amino group in thebenine is secondary in nature. Methebenine, ethebenine and prothebenine degrade similarly to methebenol, ethebenol and prothebenol (4).

The investigations of Freund and Pschorr have shown thebenine and thebenol to have the following structures:

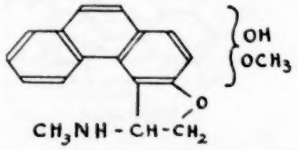


Thebenine

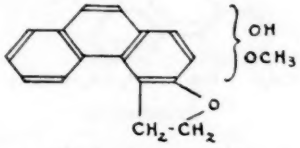


Thebenol

Reasoning from the supposed existence of an oxazine ring in thebaine (p. 337), Freund developed for thebenine and thebenol the formulas:



Thebenine (Freund)

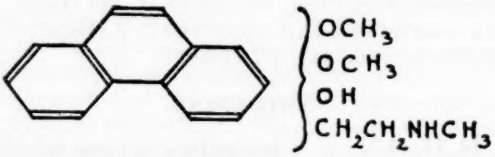


Thebenol (Freund)

Methebenine, the monomethyl ether of thebenine, was found however by Pschorr and Massaciu (6) to be a phenolic substance, whence the

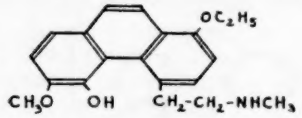
* See Appendix, p. 368.

third oxygen of methebenine could not be bound in an ether ring. Methylation of the hydroxyl in methebenine and degradation led through a trimethoxyvinylphenanthrene to a trimethoxyphenanthrene carboxylic acid. Methebenine was thus resolved into a phenanthrene nucleus carrying two methoxyls, a hydroxyl, and a methylaminoethyl group:

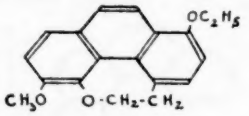


Pschorr reasoned that in thebenine, as in morphothebaine, the methoxyl and one hydroxyl probably occupied positions 3 and 4, respectively; the observation of Freund (7) (8) and Vongerichten (9) that pyrene was formed as a product of violent reduction (zinc dust distillation, phosphorous and hydriodic acid) of thebenine or thebenol made an attachment of the aminoethyl group at C-5 seem probable, and finally the preparation of thebenine from codeinone and pseudocodeinone fixed the second hydroxyl at C-6 or C-8. Decarboxylation of the above-mentioned trimethoxyphenanthrene carboxylic acid gave, in fact, 3, 4, 8-trimethoxyphenanthrene; the three oxygen atoms in thebenine are in the 3, 4, 8-positions (10).

Additional support for locating the nitrogen chain on C-5 was obtained from a study of the thebenol ring closure. The ethanamine chain of thebenine must lie in a position very favorable to formation of an ether ring with one of the hydroxyl groups during degradation; determination of the hydroxyl involved, which limited the possible locations for the nitrogen chain, was accomplished as follows. Thebenine ethyl ether, ethebenine, undergoes a thebenol ring closure during degradation. In ethebenol and ethebenine the ethoxyl group is on C-8, as was shown by conversion to the synthetic 3, 4-dimethoxy-8-ethoxyphenanthrene (10) (11). Ring formation to ethebenol must take place therefore with the hydroxyl on C-4, since C-8 is occupied by the ethoxyl. On steric grounds, only C-5 comes into consideration as the point of attachment of the C–C–N chain.



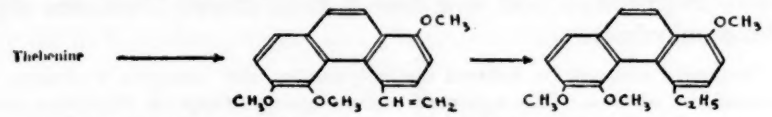
Ethebenine



Ethebenol

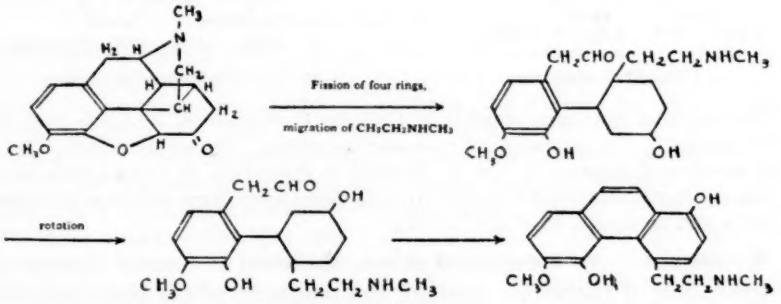
A strict proof of the position of the nitrogen chain in thebenine is offered by the recent work of Gulland and Virden (12). After an attempt to identify 3, 4, 8-trimethoxyphenanthrene-5-carboxylic acid by conversion to the tetramethoxy compound over the azide had failed, these investigators found that the trimethoxyvinylphenan-

threne resulting from methylation and degradation of thebenine can be reduced to 3, 4, 8-trimethoxy-5-ethylphenanthrene, identical with the compound obtained through the Pschorr phenanthrene synthesis from 2-nitroveratraldehyde and 6-methoxy-3-ethylphenylacetic acid.

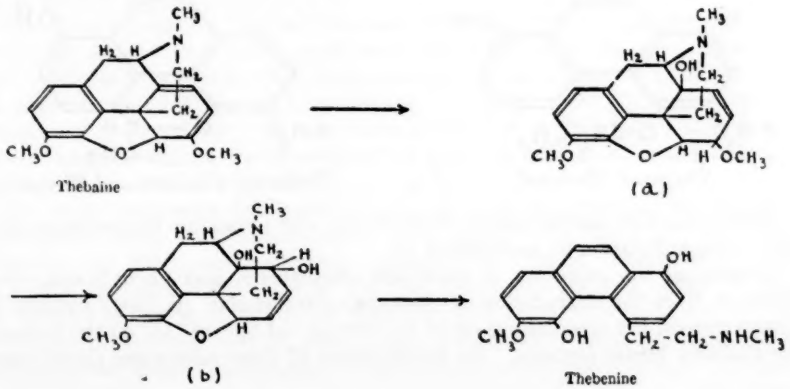


Trimethoxyvinylphenanthrene Trimethoxyethylphenanthrene

The mechanism first suggested for the thebaine-thebenine change involved hydrolytic opening of the nitrogen ring and bridge bonds in the Freund bridge-linkage formula for thebaine (13). Gulland and Robinson (14) proposed tentatively a complicated ring opening of codeinone (from hydrolysis of thebaine) with rotation of ring III, followed by ring closure:

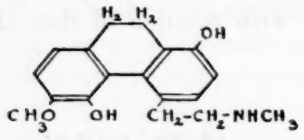


Schöpf and Borkowsky (15) believe that a 1, 4-addition of water or acid to thebaine takes place, with formation of an α, β-unsaturated ether, which with simultaneous hydrolysis, undergoes the codeinone-pseudocodeinone rearrangement. By this the impetus for aromatization is given, the ether bridge opens, the ethanamine chain must move, and shifts to the neighboring C-5. For steric reasons nitrogen must now break from C-9, and ring II becomes thereby aromatic:

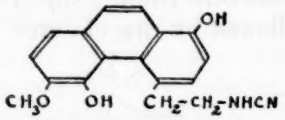


While Schöpf's proposal constitutes the most reasonable explanation yet advanced for this change, Gulland and Virden (12) point out that the hydrolyzed form of (*a*) above is the formula assigned to 14-hydroxycodeine (p. 256) and that this substance is not affected by hot dilute hydrochloric acid, nor does it yield triacetylthebenine with acetic anhydride.

Thebenine can not be reduced electrolytically, with catalytic hydrogen, or sodium and alcohol. The action of sodium hydrosulphite on thebenine gives dihydrothebenine (16), in which the 9, 10-double linkage is believed to be saturated. Exhaustive methylation of this was unsuccessful, but the dimethyl ether could be degraded to dihydrothebenol methyl ether (methoxydihydrothebenol). The vinyl compound resulting from degradation evidently reacts with the methoxyl group on C-4, setting up the thebenol ether ring, as Pschorr (6) (10) showed to be the case with 3, 4, 8-trimethoxy-5-vinylphenanthrene.



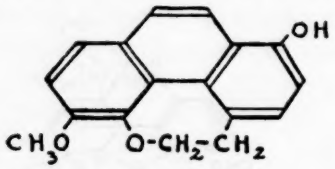
Dihydrothebenine



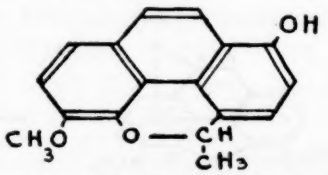
Cyanonorthebenine

The action of cyanogen bromide on thebaine in chloroform, or acetic acid (17) (18), results in the formation of cyanonorthebenine. By catalytic reduction of this substance, apparently the 9, 10-bond is saturated, and the cyano group reduced; the resulting $-CH_2CH_2NHCH_2NH_2$ chain hydrolyzes with loss of formaldehyde and ammonia, to $-CH_2CH_2NH_2$.

THEBENOL. As mentioned above, thebenol is formed during the degradation of thebenine through the tendency of the intermediately formed vinyl group to react with a neighboring hydroxyl to give a cyclic ether grouping (19). This reaction, together with the transformation of thebenol to pyrene on zinc dust distillation (7) (*cf.* Jürst (20), Freund (21)) gave the first hint regarding the position of the ethanamine chain in thebenine. Because of the ease of formation, and greater stability of 6-membered oxide rings, Gulland and Virden (12) have modified the thebenol formula of Pschorr (10).



Thebenol (Pschorr)



Thebenol (Gulland and Virden)

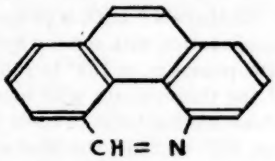
Thebenol is very stable toward alkali; fusion with potassium hydroxide results only in demethylation to northebenol (7).

Concerning the structure of phenyldihydrothebenol and phenyltetrahydrothebenol, from the degradation of phenyldihydrothebaine (p. 334), nothing is known beyond the speculations given by Freund and Speyer (13) on the basis of the thebaine bridge formula. An investigation of these substances should give

valuable evidence on the structure of phenyldihydrothebaine. Phenyldihydrothebenol forms two isomeric methyl ethers (22).

The so-called oxymethebenol obtained as a by-product in the oxidation of 3, 4, 8-trimethoxy-5-vinylphenanthrene (10) was shown by Gulland and Virden (12) to be actually 3, 4, 8-trimethoxyphenanthrene-5-aldehyde.

THEBENIDINE. The zinc dust distillation of thebenine yields not only the hydrocarbon pyrene, but a basic substance, thebenidine (9).



As would be expected from this formula, thebenidine resembles phenanthridine and chrysidine closely in properties. In a gentler reaction, dehydration of 3, 4, 8-trimethoxyphenanthrene-5-aldehyde oxime, what appears to be 3, 8-dimethoxythebenidine was obtained (12).

Descriptive Part (Thebenine)

THEBENINE: B=$C_{18}H_{19}O_3N$. Prep.: 10 g. of thebaine is added to 100 c. c. of nearly boiling hydrochloric acid of sp. gr. 1.07 and the solution boiled for 1½ to 2 min. The solution is cooled strongly and ice added, whereby thebenine hydrochloride separates as a resin. This may be crystallized from hot water, yield about 6 g. (7). The free base is precipitated amorphous from its salts by sodium sulphite; it is insoluble in ether, benzene, or ammonia, sparingly sol. in boiling alcohol. It is very soluble in alkali, and oxidizes rapidly in such solutions. Conc. H_2SO_4 gives a magnificent blue color with thebenine or its salts; the color disappears on dilution with water (1). —HYDROCHLORIDE, B·HCl+$3H_2O$, pale yellow crystals, becoming gray on drying, sinters 231°, melts 235°; bitter in taste. Soluble in boiling water or alcohol (1) (7). The PLATINICHLORIDE is amorphous, the MERCURICHLORIDE (+H_2O) consists of colorless fan-shaped aggregates of prisms. —SULPHATE, B_2·H_2SO_4+H_2O, quadratic yellow leaflets, sparingly sol. in hot water; sinters 205°, melts 209° to 210° (1) (7). —THIOCYANATE, white cryst. powder (1). —OXALATE, B·$C_2H_2O_4$+H_2O, grouped needles, m. p. 275° to 276°, cryst. from water; insol. in alcohol.

THEBENINEMETHINE METHIODIDE: $C_{20}H_{24}O_3NI$, results from refluxing thebenine with methyl iodide, or in better yields from thebenine hydrochloride and methyl iodide in the presence of two moles of sodium ethylate. Cryst. from alcohol, m. p. 206° to 208° (7).

THEBENINE-8-METHYL ETHER (Methebenine): $C_{19}H_{21}O_3N$, from thebaine with methyl alcoholic HCl at 100°; cryst. from alcohol, m. p. 165° to 167°. Hot 20% HCl converts it to thebenine. METHEBENINE HYDROCHLORIDE m. 250° (corr.); HYDRIODIDE m. 195° to 198°, SULPHATE m. 238.5° (corr.). The DIACETYL Derivative melts at 176°, the DIBENZOYL Derivative at 159° (corr.) (2) (4) (6). METHEBENINEMETHINE METHIODIDE cryst. from dil. alcohol, m. p. 215°, gives a Benzoyl Derivative of m. p. 271° (corr.) (4) (6).

THEBENINE-4,8-DIMETHYL ETHER is known only as dimethebeninemethine methiodide, from methebeninemethine methiodide with alkali and dimethyl sulphate; the Methomethylsulphate which is first obtained, consists of cryst. of m. p. 277° (corr.), and gives with KI the Methiodide, needles of m. p. 247° (corr.). It degrades to 3, 4, 8-trimethoxy-5-vinylphenanthrene (6) (10) (12).

THEBENINE-8-ETHYL ETHER (Ethebenine): $C_{20}H_{23}O_3N$ from thebaine with ethyl alcoholic HCl, is amorphous. The HYDROCHLORIDE cryst. from dil. alcohol,

m. p. 248°, HYDRIODIDE ($+H_2O$) m. p. 206° to 207°; DIACETYL Derivative, m. p. 163°; ETHEBENINEMETHINE METHIODIDE melts at 215° (4).

THEBENINE-4-METHYL-8-ETHYL ETHER (Methethebenine) was obtained in the form of the methomethylsulphate, needles of m. p. 241° (corr.); the METHIODIDE melts at 252° (corr.) (10).

THEBENINE-8-PROPYL ETHER (Prothebenine): $C_{21}H_{25}O_3N$, crystallizes from alcohol, m. p. 172° to 173°. The HYDROCHLORIDE m. 220° to 221°, the HYDRIODIDE m. 212° to 213°, and the METHINE METHIODIDE m. 202° (4).

DIHYDROTHEBENINE (16): $C_{18}H_{21}O_3N+H_2O$, is prepared from thebenine hydrochloride by reduction in boiling solution with sodium hydrosulphite. The product is obtained as the thiosulphate, prisms m. p. 194° to 195°. The free base is precip. from an acetone solution of the thiosulphate with ammonia, and cryst. in rods, decomp. at 147° to 148°, which are insoluble in most media. The HYDROCHLORIDE, yellow leaflets, decomp. 237° to 238°, the METHIODIDE (N-methyldihydrothebenine hydriodide) leaflets from water, m. p. 130° to 131°. The DIMETHYL ETHER METHINE METHOSULPHATE decomp. 270° to 271°, its Methiodide decomp. 245°.

CYANONORTHEBENINE (17) (18): $C_{18}H_{16}O_3N_2$, from thebenine in acetic acid with CNBr. Leaflets from alcohol, m. p. 146° to 147°. It could not be saponified; catalytic hydrogenation gave a compound whose Methiodide, $C_{20}H_{26}O_2NI$, melted at 298° to 299°.

TRIACETYLTHEBENINE, from the action of acetic anhydride on thebenine (4), codeinone (2), or pseudocodeinone (3), cryst. from alcohol m. p. 160° to 161°.

THEBENYLPHENYLTHIOUREA: $C_{18}H_{18}O_3NCSNHC_6H_5$, from thebenine with phenylisothiocyanate, cryst. of m. p. 85° (7).

THEBENOL: $C_{17}H_{14}O_3$, from thebeninemethine methiodide with alkali, crystallizes from alcohol, ether, chloroform, or benzene, m. p. 186° to 188°; it is soluble in alkali. SODIUM SALT, m. p. 210° to 212°. ACETYL Derivative m. p. 102° to 103° (5) (7).

METHEBENOL (Thebenol methyl ether), plates from glacial acetic acid, m. p. 133° to 134°, PICRATE, m. p. 106° (4) (6) (7). OXYMETHEBENOL (10), see Gulland and Virden (12).

ETHEBENOL (Thebenol ethyl ether), from degradation of ethebeninemethine methiodide, cryst. from acetic acid, m. p. 103° to 105° (4). OXYETHEBENOL (10), see methebenol above.

PROTHEBENOL (Thebenol propyl ether), cryst. from acetic acid, soften 99°, m. p. 103° to 105° (4).

NORTHEBENOL: $C_{16}H_{12}O_3$, from demethylation of thebenol with 30% KOH, cryst. from acetic acid, m. p. 202° to 203°. It gives a compound with hydriodic acid which decomp. 270° (7).

DIHYDROTHEBENOL METHYL ETHER, m. p. 133° to 134° (16).

PHENYLDIHYDROTHEBENOL: $C_{23}H_{20}O_3$, from exhaustive methylation of phenyldihydrothebaine; cryst. from alcohol, m. p. 148° to 149°. Its METHYL ETHER occurs in two forms, m. p. (α) 114° to 115°, (β) 123° to 124°; ETHYL ETHER, m. p. 97° to 98° (22); DICHLORO Derivative, needles m. p. 160° to 162° (13). PHENYLTETRAHYDROTHEBENOL, m. p. 86° (13).

THEBENIDINE: $C_{15}H_9N$, from zinc dust distillation of thebenine; cryst. from benzene, m. p. 144° to 148°. The METHIODIDE melts at 240° (9); 3, 8-DIMETHOXY Derivative (?) orange leaflets, m. p. 229° to 230°, whose Picrate decomp. 255° (12).

THEBAICINE (1) is a yellow amorphous substance obtained from the action of conc. HCl on thebenine or thebaine. It is insol. in ether, benzene, water, or ammonia, sparingly sol. in hot alcohol; soluble in alkali, absorbs oxygen. It gives with conc. HNO_3 a dark red solution, with conc. H_2SO_4 a dark blue solution. The salts are all amorphous. It was regarded by Hesse as an isomer of thebenine.

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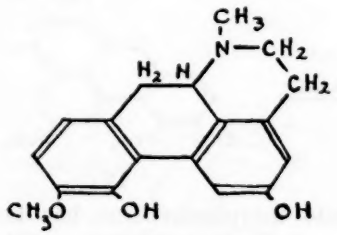
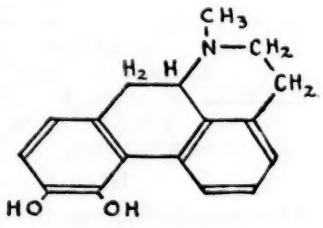
MORPHOTHEBAINE

Morphothebaine, $C_{17}H_{17}O_3N$, is formed by the action of hot concentrated hydrochloric acid on thebaine (1) or on codeinone (2). Howard and Roser (3) believed it to be merely a demethylated thebaine. Freund (4) showed, however, that it could not be converted back to thebaine, and expressed the view that a rearrangement had taken place, in which Howard's "acid hydrochloride" (see below) possibly played a part. Speculations on the mechanism of the change were given in a later publication (5).

Morphothebaine is, in fact, closely similar in structure to apomorphine, as Pschorr was able to show by the same methods as were employed with that base (p. 261).



Morphothebaine



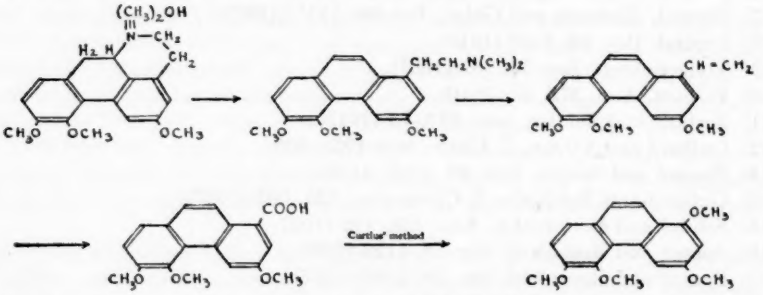
Apomorphine

Morphothebaine suffers scission of the nitrogen ring on heating with benzoyl chloride, yielding a tribenzoyl derivative (6)[6] which, like the

[6] A triacetyl derivative was obtained six years earlier by Freund (4), who did not realize its significance.

tribenzoyl compound from apomorphine, can be oxidized to a phenanthrenequinone with no loss of groups (7), showing that the 9, 10-positions are free after benzoylation.

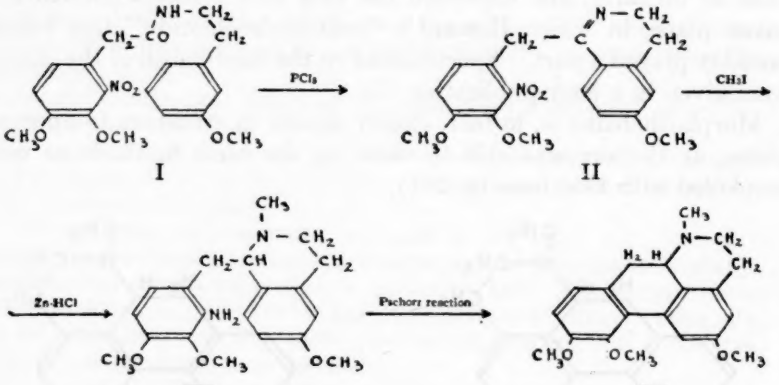
Exhaustive methylation of morphothebaine dimethyl ether resulted in a trimethoxyvinylphenanthrene (6), which could be converted to 3, 4, 6, 8-tetramethoxyphenanthrene (8).



The synthesis of this substance by Pschorr and Knöffler (9) made certain the position of every group in the morphothebaine molecule.

Morphothebaine dimethyl ether has been synthesized by Gulland and Haworth (10):

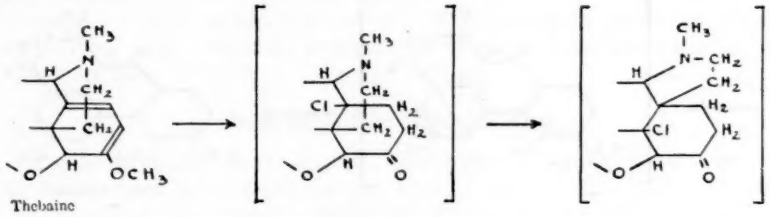
2′-Nitro-3′,4′-dimethoxyphenylaceto-β-3-methoxyphenylethylamide (I) was converted to the isoquinoline derivative (II) by the action of phosphorous pentachloride. Reduction of the methiodide of this with zinc and hydrochloric acid gave 2′-amino-6,3′,4′-trimethoxy-1-benzyl-2-methyltetrahydroisoquinoline (III) which was condensed by the method of Pschorr to racemic 3, 4, 6-trimethoxyaporphine (IV). The levo form of this is identical with morphothebaine dimethyl ether.



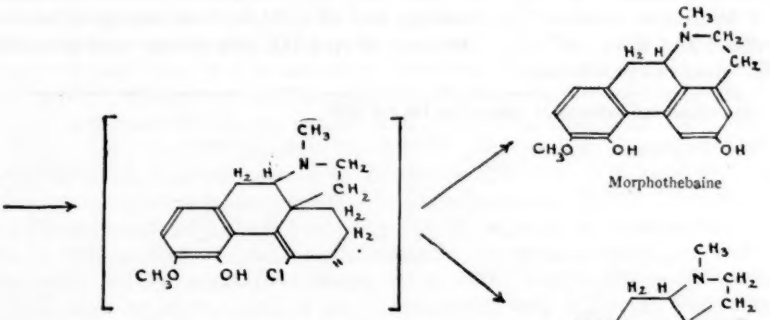
The transformation of thebaine into morphothebaine has been extensively investigated by Schöpf and Borkowsky (11). When thebaine is dissolved in cold concentrated hydrochloric acid, a deep orange-red solution results, from which neither thebaine nor morphothebaine can be isolated. The color is due to halochromism, and fades out on dilution with water, to reappear with addition of more hydro-

chloric acid. When the red solution is heated to 100° the color disappears, and Howard's so-called "acid hydrochloride" crystallizes out in 80% to 85% yield. This is the acid hydrochloride of morphothebaine, and with its appearance the transformation of thebaine to morphothebaine is completed.

The halochromic hydrochloric acid solution yields neither thebaine nor morphothebaine, hence it must contain some intermediate substance, which is probably closely related to thebainone, since Pschorr (12) obtained the latter by reduction of the red solution. (See thebainone, p. 308.) The absorption spectra of thebaine and of thebainone in concentrated hydrochloric acid are closely similar. From these considerations, and in view of work on the structure of thebainone, Schöpf believes that the shift of the side chain from C-13 to C-8 takes place in steps. The conversion is accounted for as pictured below: hydrolysis of the enol ether group and addition of hydrogen chloride are followed by a retropinacone rearrangement, whereby the chlorine and the side chain change places. The β-chloroketone, with a tertiary linked halogen suffers a shift of hydrogen chloride, which goes to open the ether bridge, and the thebainonelike intermediate appears. Finally, loss of hydrogen chloride under reducing conditions yields thebainone, or without reduction, morphothebaine.



Thebaine

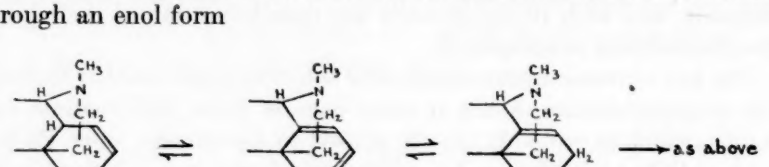


Morphothebaine

Thebainone

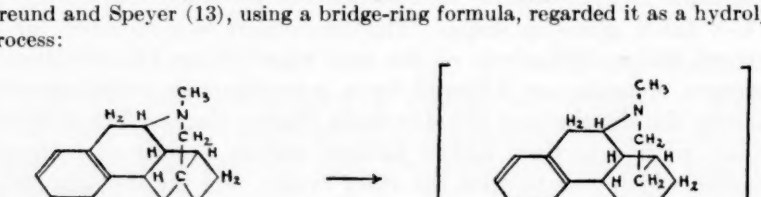
The shift from C-13 to C-8 takes place as the result of a tendency of the system to become aromatic under the influence of acid.[7]

The same mechanism accounts for the transformation of codeinone through an enol form

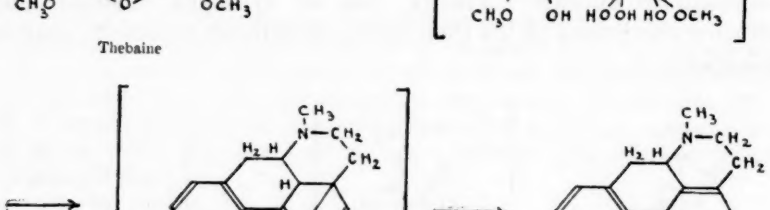


to morphothebaine.

Various other explanations of the process have appeared in the literature. Freund and Speyer (13), using a bridge-ring formula, regarded it as a hydrolytic process:



Thebaine

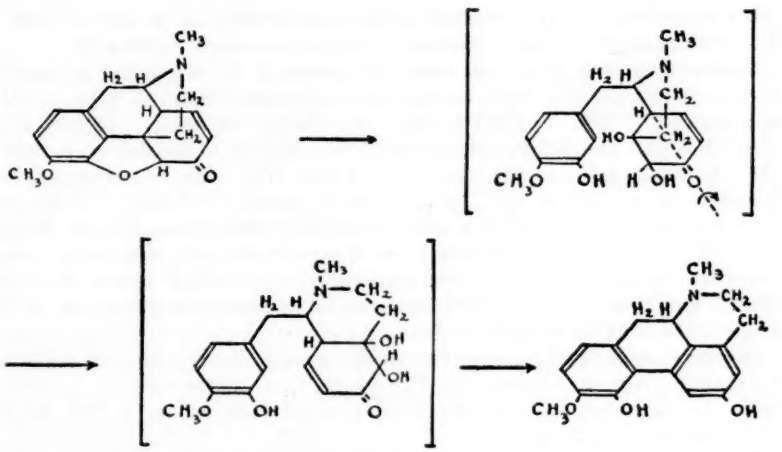


Morphothebaine

Wieland and Kotake (14) likewise represented the change as taking place through a bridge-ring stage from codeinone, formed by hydrolysis of thebaine.

A hydrolytic break of the O-bridge and of C-12 to C-13 was postulated by Gulland and Robinson (15). Rotation of ring III, ring closure and aromatization, gives morphothebaine:

[7] See Gulland and Robinson, J. Chem. Soc. **123**, 992 (1923).



Faltis (16) explains the change by a hydrolysis of the C-4 to C-8 oxygen bridge (Faltis formula, p. 345), followed by rearrangement through an ethanolamine intermediate, and ring closure to morphothebaine.

Morphothebaine can be demethylated with dilute hydrobromic acid at 170°. The product is 6-hydroxyapomorphine (17). (See apomorphine, p. 263.)

Morphothebaine gives the following color reactions: concentrated sulphuric acid, colorless; concentrated nitric acid, blood-red, red-brown, becoming lighter; Erdmann's reagent, pale yellow, reddish; Fröhde's reagent, steel-blue, gray-blue with violet tinge; Mandelin's reagent, dirty violet with little reagent, brown with much reagent (18).*

Descriptive Part (Morphothebaine)

MORPHOTHEBAINE: B=$C_{18}H_{19}O_3N$. Prepared by heating thebaine at 80° to 90° for one hour in a sealed tube with 10 to 15 parts of 38% HCl. (*Cf.* ref. 6.) The crystalline acid hydrochloride is washed with cold conc. HCl and absol. ether. Yield, 80% to 85% (11). The acid hydrochloride is converted to the neutral hydrochloride by boiling with alcohol, the free base precip. from aqueous solution of the hydrochloride with Na_2CO_3 and extracted with ether. It is purified once more through the hydrochloride, and isolated from ether. Klee (18) obtained 6.5 g. of base from 10 g. of thebaine. The base is sparingly soluble in methanol or benzene, moderately sol. in xylene or nitrobenzene (4), soluble in alkali. It cryst. in rhombic bluish or green crystals, white when fresh, m. p. 197° (decomp.) (2) (18); $[\alpha]_D^{15} = -130°$ (alcohol, C=0.8848) (18). —ACID HYDROCHLORIDE (1), $(B{\cdot}HCl)_2HCl$, colorless needles, m. p. 254° to 255° (11). It loses HCl readily to give the neutral hydrochloride. —HYDROCHLORIDE, B·HCl, from treatment of the acid salt with alcohol or water (1) (4); microscopic needles from water, m. p. 256° to 260°. —ACID HYDROBROMIDE (1), granular crystals. —HYDROBROMIDE, B·HBr. cryst. from water, m. p. 270° to 275° (4). —HYDRIODIDE, B·HI, from an aqueous sol. of the hydrochloride with KI, cryst. from very dil. alcohol in needle clusters, m. p. 243° to 244° (soften at 237°) (4). —NITRATE (1), $B{\cdot}HNO_3+2H_2O$, from treatment of the hydrochloride with $AgNO_3$, white crystal clusters. —SULPHATE (1), $B_2{\cdot}H_2SO_4+7H_2O$, monoclinic prisms. The PICRATE and OXALATE are described as amorphous (1).

*See Appendix, p. 368.

—METHIODIDE: B·CH_3I, crystallizes from acetic acid, m. p. 221° to 222° (3) (4). —ETHIODIDE, rhombic crystals. —BENZOCHLORIDE, needles (3).

MORPHOTHEBAINE DIMETHYL ETHER is prepared by treatment of morphothebaine in isoamyl ether with nascent diazomethane; it is an oil, $[\alpha]_D = -184.8°$ (approximate) (18), −172.7° (10). Synthetic material, $[\alpha]_D = -173.5°$ ($CHCl_3$) (10). The *d*-BITARTRATE cryst. from alcohol in needles m. p. 208° to 209° (decomp.), $[\alpha]_D = -75°$ (water, C=1.040) (10). The METHIODIDE cryst. in needles, m. p. 190° to 195°, $[\alpha]_D = -88.2°$ (water, C=0.533). *d,l*-MORPHOTHEBAINE DIMETHYL ETHER (3, 4, 6-trimethoxyaporphine) forms a cryst. HYDRIODIDE, of m. p. 227° (decomp.). *d*-MORPHOTHEBAINE DIMETHYL ETHER *l*-BITARTRATE melts at 208° to 209° (decomp.), $[\alpha]_D = +75.5°$ (water, C=0.821) and the free base from this, *d*-MORPHOTHEBAINE DIMETHYL ETHER, an oil, has $[\alpha]_D = +174.2°$ ($CHCl_3$) (10).

DIMETHYLMORPHOTHEBAINEMETHINE METHIODIDE, from action of CH_3I and $NaOCH_3$ on morphothebaine (6) (8). Cryst. from acetic acid, m. p. 266° to 268°. It degrades to trimethoxyvinylphenanthrene of m. p. 60° to 61°, whose Picrate m. 125° to 126°.

TRIACETYLMORPHOTHEBAINE, from refluxing morphothebaine hydrochloride with acetic anhydride and sodium acetate; it cryst. from dil. alcohol, m. p. 193° to 194° (4). Howard (1) described a Monoacetyl compound, m. p. 183°.

TRIBENZOYLMORPHOTHEBAINE, cryst. from alcohol, m. p. 184° (corr.) (7); from ether, it cryst. with solvent, m. p. 120°, solidifying and remelting at 181° (6). By oxidation it is converted to the QUINONE, an oil whose PHENYLHYDRAZONE m. 227° (corr.) and Azine m. 201° (corr.). The quinone with NaOH gives N-Benzoylmorphothebainequinone, m. p. 267° (7).

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(10) Gulland and Haworth, J. Chem. Soc. **1928,** 2083.
(11) Schöpf and Borkowsky, Ann. **458,** 148 (1927).
(12) Pschorr, Ber. **38,** 3160 (1905).
(13) Freund and Speyer, Ber. **49,** 1287 (1916).
(14) Wieland and Kotake, Ann. **444,** 69 (1925).
(15) Gulland and Robinson, Mem. Proc. Manchester Lit. Phil. Soc. **69,** 79 (1925).
(16) Faltis, Arch. Pharm. **255,** 85 (1917).
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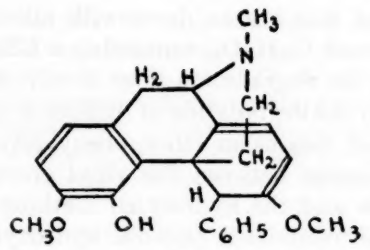
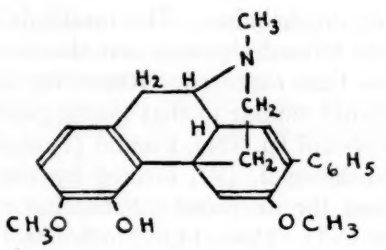
(18) Klee, Arch. Pharm. **252,** 211 (1914).

PHENYLDIHYDROTHEBAINE

Thebaine reacts with phenyl magnesium bromide to give a product which contains a phenyl group and one hydrogen atom more than thebaine, and which was therefore named by Freund (1) phenyldihydrothebaine. Its phenolic character shows that the 4, 5-ether bridge has been opened; the location of the phenyl group is not certain, but it is believed to be on C-5 or C-7 (formulas I and II, respectively).

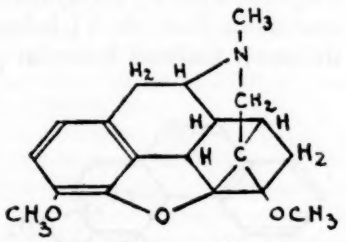


I

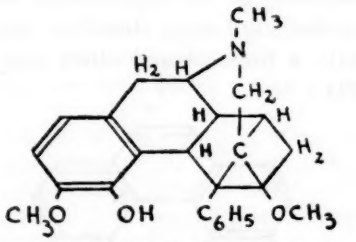


II

The most striking characteristic of phenyldihydrothebaine is its extreme resistance to reagents which usually attack the double linkage. This peculiarity led Freund to propose for it, and for the parent substance, thebaine, a bridge-linkage formula containing no double bonds in the hydrogenated ring (2).



III. Thebaine (Freund)



IV. Phenyldihydrothebaine

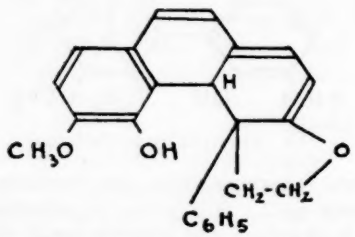
Phenyldihydrothebaine is unaffected by most reducing agents; even the powerful electrolytic method of Tafel leaves it unchanged. With colloidal palladium and hydrogen, one molecule of hydrogen is absorbed, but goes to break the ethanamine chain, forming phenyltetrahydrothebaimine, a secondary base (2). Phenyldihydrothebaine methyl ether is unaffected by vigorous treatment with ozone (3).

In contrast to thebaine, phenyldihydrothebaine is exceedingly stable toward acids or alkali. Even heating with concentrated hydrochloric acid under pressure causes no greater change than splitting the two methoxyl groups, yielding norphenyldihydrothebaine. Boiling with acetic anhydride, which breaks thebaine down to acetylthebaol (p. 294), merely gives an acetyl derivative of phenyldihydrothebaine (1) (4).

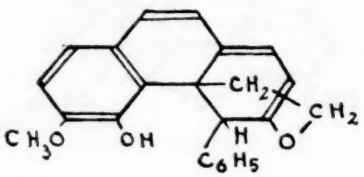
In the light of the Robinson formula the extreme stability of phenyldihydrothebaine is difficult to explain; if, however, addition of phenyl magnesium bromide to thebaine has taken place in such a way (i. e., in the 1, 6-positions) that the phenyl group is on C-14, then the tendency for changes which depend upon aromatization of ring III to take place is greatly reduced, since both the ethanamine chain and the phenyl group must be moved before the ring can become aromatic. The indifference of the unsaturated linkages in ring III remains unexplained.

Degradation of phenyldihydrothebaine by exhaustive methylation proceeds at first normally, with the formation of des-N-methylphenyl-

dihydrothebaine. The methiodide of this breaks down with alkali into trimethylamine, and the compound $C_{23}H_{20}O_3$, containing a CH_2 less than expected. Reasoning that the degradation must involve a change similar to that taking place in the degradation of thebenine to thebenol (p. 324), Freund (1) regarded this as an ether, phenyldihydrothebenol, (V), formed by ring closure between the vinyl group from the degraded ethanamine chain and the hydrolyzed methoxyl on C-6.[8] Phenyldihydrothebenol still contains a phenolic hydroxyl, and yields a methyl ether, which may also be obtained from degradation of phenyldihydrothebaine methyl ether. When phenyldihydrothebaine-4-ethyl ether is degraded, the ethyl group is still present in the resulting thebenol product, hence the methoxyl group on C-6 is the one involved in the ether formation. There is no reason to expect the ethanamine bridge to shift from the 13-position (Robinson formula) in the degradation of phenyldihydrothebaine; phenyldihydrothebenol may therefore be constituted as in Formula VI below, with a 6-membered ether ring. (*Cf.* thebenol, Gulland formula, p. 324.)



V. Phenyldihydrothebenol (Freund)



VI. Phenyldihydrothebenol

Phenyldihydrothebenol methyl ether is changed into an isomer on heating, perhaps due to a shift of a double linkage (1), or to a cis-trans shift of the phenyl group (2).

Phenyldihydrothebaine reacts with halogen giving a dichloro- or dibromo-derivative in poor yield. The location of the halogen is not known. Dichlorophenyldihydrothebaine has been degraded to dichlorophenyldihydrothebenol. By electrolytic reduction of dibromophenyldihydrothebaine, phenyltetrahydrothebaine was obtained (2).

Oxidation of phenyldihydrothebaine with hydrogen peroxide results in phenyldihydrothebaine carboxylic acid, of whose structure little is known (2).

Benzyl magnesium chloride reacts with thebaine to give benzyldihydrothebaine (5).

Descriptive Part (Phenyldihydrothebaine)

PHENYLDIHYDROTHEBAINE: $B=C_{25}H_{27}O_3N$, prep. by reaction of thebaine and phenyl magnesium bromide, isolated as the hydriodide, from which dilute alkali and ammonium chloride precipitate the free base; cryst. from alcohol, m. p.

[8] The tendency to close an ether ring is so great in the case of certain methoxyvinylphenanthrenes that hydrolysis of a methoxyl group and ether formation takes place when the substance is dissolved in warm acetic acid, as Pschorr (Ber. 37, 2790 (1904); Ann. 373, 73 (1910)) showed in the case of 3, 4, 8-trimethoxy-5-vinylphenanthrene and 3, 4-dimethoxy-8-ethoxy-5-vinylphenanthrene.

60° to 65°. It is very soluble in all organic solvents; with conc. sodium hydroxide it gives a cryst. sodium salt (1). —HYDROCHLORIDE, prisms from alcohol, B·HCl+C_2H_5OH, m. p. 145° to 147°; cryst. from water, m. p. 165°; $\alpha = -1.57°$ (4% aqueous solution). —HYDROBROMIDE, cryst. from water in plates, decomp. 190° to 195°. —HYDRIODIDE, cryst. from water, m. p. 230° to 232°, from alcohol (+C_2H_5OH), m. p. 182° to 184° (1) (5).

PHENYLDIHYDROTHEBAINE METHIODIDE: B·CH_3I, cryst. from dil. alcohol, m. p. 230° to 231° (1). It gives with alkali DES-N-METHYLPHENYLDIHYDROTHEBAINE, $C_{26}H_{29}O_3N$, m. p. 90°, whose Methiodide melts at 145° to 155°, and degrades to the compound $C_{23}H_{20}O_3$, PHENYLDIHYDROTHEBENOL, which cryst. from alcohol in plates of m. p. 148° to 149°, soluble in alkali.

PHENYLDIHYDROTHEBAINE METHYL ETHER, m. p. 70°; its METHIODIDE, m. p. 209° to 210°, degrades to DES-N-METHYLPHENYLDIHYDROTHEBAINE METHYL ETHER, an oil, whose amorph. Platinichloride melts 125° to 135°, and whose Methiodide decomp. with alkali to α-PHENYLDIHYDROTHEBENOL METHYL ETHER, m. p. 114° to 115°, which isomerizes on heating over the m. p. to the β-form, m. p. 123° to 124°.

PHENYLDIHYDROTHEBAINE ETHYL ETHER. —METHIODIDE, m. p. 209° to 210°, degrades to the corresponding DES-N-METHYLPHENYLDIHYDROTHEBAINE ETHYL ETHER, whose Methiodide cryst. from absol. alcohol in plates, m. p. 247° to 248°. The latter gives with alkali PHENYLDIHYDROTHEBENOL ETHYL ETHER, rods, m. p. 97° to 98° (1).

ACETYLPHENYLDIHYDROTHEBAINE, sinters at 65° to 70°, melts at 92°. Its METHIODIDE cryst. from alcohol in rods, m. p. 202° to 203° (1). An unidentified product was obtained by the action of BrCN on acetylphenyldihydrothebaine (2).

NORPHENYLDIHYDROTHEBAINE: $C_{23}H_{23}O_3N$, from boiling phenyldihydrothebaine hydriodide with hydriodic acid; the HYDRIODIDE melts 185° to 190°, the HYDROCHLORIDE cryst. in white needles which sinter 190° to 200° and decomp. 200° to 220°. The free base cryst. from hot water in needles sintering at 120° to 125°. It dissolves in NaOH to give a solution with an odor as of benzaldehyde (1).

DICHLOROPHENYLDIHYDROTHEBAINE (2), from treatment of phenyldihydrothebaine with hot HCl and H_2O_2; isolated as the HYDRIODIDE, which sinters 185°, melts (decomp.) at 203°. The free base, cryst. from alcohol, sinters 130°, melts unsharp 135° to 140°. Its METHIODIDE cryst. from acetic acid, m. 230°. The methiodide degrades to DES-N-METHYLDICHLOROPHENYLDIHYDROTHEBAINE, an oil, whose Hydriodide melts ca. 205°, and whose Methiodide degrades to DICHLOROPHENYLDIHYDROTHEBENOL, m. p. 160° to 162°.

DIBROMOPHENYLDIHYDROTHEBAINE (2), from action of bromine in acetic acid on phenyldihydrothebaine; the perbromide formed cryst. from acetic acid m. p. 195° to 196°. Digested with SO_2 in alcohol, it gives the hydrobromide, decomp. 198°. The free base, cryst. from alcohol, m. p. 165° to 168° (unsharp); its HYDRIODIDE decomp. 205° to 208°.

PHENYLTETRAHYDROTHEBAINE (2), prep. by electrol. reduction of dibromophenyldihydrothebaine; isolated as the HYDROBROMIDE, decomp. 175° to 176°. The free base is an oil, which gives a METHIODIDE of m. p. 215°. By boiling the methiodide with conc. HI, NORPHENYLTETRAHYDROTHEBAINE HYDRIODIDE, needles from water, decomp. 195°, is obtained.

PHENYLDIHYDROTHEBAINE CARBOXYLIC ACID (2): $C_{24}H_{23}O_5N$, from treatment of phenyldihydrothebaine with H_2O_2 in alkaline solution, prisms, decomp. 243° to 245°. The Ba salt cryst. in needles, decomp. 280°.

PHENYLTETRAHYDROTHEBAIMINE (2): $C_{25}H_{29}O_3N$, prep. by reduction of phenyldihydrothebaine in dil. acetic acid with colloidal palladium and hydrogen. It cryst. from alcohol in quantitative yield in leaflets of m. p. 122°; $[\alpha]_D^{20} = +27.6°$ (dil. acetic acid, C=5.065). It is alkali-soluble, gives no cryst. salts with acids.

The NITROSO derivative decomp. 193°. BIS-PHENYLTETRAHYDROTHEBAIMINE UREA (from treatment with $COCl_2$), needles, m. p. 138° to 139°. With methyl iodide PHENYLTETRAHYDROTHEBAIMINEMETHINE METHIODIDE is formed, m. p. 233° to 235°, which degrades to PHENYLTETRAHYDROTHEBENOL, m. p. 86°. The same product is obtained by degradation of the addition-product of methyl-p-toluenesulphonate and phenyltetrahydrothebaimine (which m. 245°, needles).

BENZYLDIHYDROTHEBAINE (5), prep. from thebaine with benzyl magnesium chloride; amorphous powder, soluble in alkali.

Bibliography (Phenyldihydrothebaine)

(1) Freund, Ber. **38**, 3234 (1905).
(2) Freund and Speyer, Ber. **49**, 1287 (1916).
(3) Wieland and Small, Ann. **467**, 17 (1928).
(4) Tiffeneau, Bull. soc. chim. (4) **17**, 109 (1915).
(5) Freund, D. R-P. 181510 (1907); Frdl. **8**, 1171.

THE CONSTITUTION OF MORPHINE

In the foregoing pages the experimental facts which have been developed in the chemistry of morphine and its related alkaloids during 125 years of research are considered in detail. In spite of numerous attempts to interpret this enormous amount of material in terms of a structural formula, the constitutional problem of morphine must still be regarded as not completely solved. The fundamental researches of Hesse, Vongerichten, Knorr, Pschorr, and Freund, which culminated in 1907 with the proposal of the Knorr-Hörlein formula, form the background for the later studies of Wieland, Speyer, von Braun, Robinson, and Schöpf. The evidence from which the most probable structural formulas have been evolved is presented briefly below.

Morphine contains a phenolic hydroxyl group; it dissolves readily in alkalies to form metallic salts in which a hydrogen atom of the base is replaced by alkali metal, and from which morphine is precipitated as the free base on treatment with carbon dioxide or ammonium chloride. Morphine gives a strong ferric chloride test.

With acid chlorides or anhydrides, morphine suffers replacement of two hydrogen atoms with acyl groups. Phosphorous pentachloride or thionyl chloride, on the other hand, yield chloromorphide, in which an -OH has been replaced by chlorine, but a phenolic hydroxyl still remains. Morphine therefore contains both a phenolic and an alcoholic hydroxyl, and the empirical formula can be resolved thus:

$$C_{17}H_{19}O_3N = HO\cdot C_{17}H_{17}ON\cdot OH$$

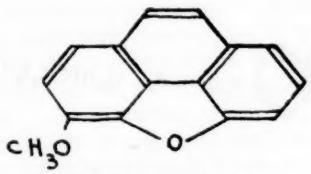
Methylation of morphine yields codeine, morphine methyl ether, which has no phenolic properties. A methyl group has been substituted for the hydrogen of the phenolic hydroxyl, but the fundamental structural skeleton is unchanged.

$$C_{18}H_{21}O_3N = CH_3O\cdot C_{17}H_{17}ON\cdot OH$$

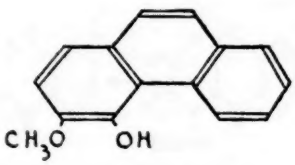
The third oxygen of morphine and codeine is inactive, and behaves as an ether oxygen. The nature of this ether linkage will be shown below.

The mode of linkage of the nitrogen atom in morphine was shown by the results of exhaustive methylation. While the methiodide of morphine itself cannot be degraded by the usual Hofmann method because of the tendency of the quaternary ammonium hydroxide to form a phenol-betaine type of compound (p. 147), such a possibility is eliminated in the case of codeine. Codeine methiodide, on boiling with dilute alkali, yields des-N-methylcodeine, α-methylmorphimethine (p. 268). The methohydroxide of α-methylmorphimethine does not break down in the manner expected in the normal course of a Hofmann degradation, but shows a striking tendency to lose the entire nitrogen-containing side chain as trimethylamine, ethylene and water. The significance of this fact will be discussed in a later paragraph (p. 350). The fact that trimethylamine is not split out of codeine methohydroxide itself, but appears first after a second methylation shows with certainty that the nitrogen in codeine and morphine is bound in a ring, and must carry a methyl group.

The nitrogen-free product which results from heating α-methylmorphimethine methohydroxide is a phenanthrene derivative, methylmorphenol, whose structure, together with that of methylmorphol (from acetolysis of certain morphine derivatives) was amply proved in the investigations of Vongerichten (p. 282).



I. Methylmorphenol



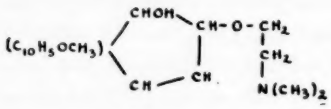
II. Methylmorphol

Evidence for the presence of a phenanthrene nucleus in morphine was also obtained from other, more vigorous reactions. Phenanthrene itself was found as the nitrogen-free product from distillation of morphine, α-methylmorphimethine or thebenine with zinc dust. The high hydrogen content of morphine and α-methylmorphimethine indicated that the phenanthrene nucleus in these bases must be partially hydrogenated (1).

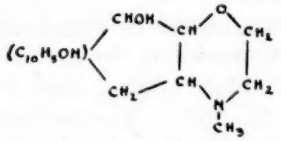
The investigations of Knorr (1) (2) first showed that of the three morphine carbon atoms not in the phenanthrene nucleus, one is on nitrogen as a methyl group, and the other two form part of a nitrogen-containing ring.

THE OXAZINE FORMULA.—The appearance of derivatives of ethanoldimethylamine, $(CH_3)_2NCH_2CH_2OH$, among the products from the degradation of α-methylmorphimethine with acetic anhydride or

sodium ethylate (p. 270) led Knorr to the belief that this alkamine must be formed through hydrolytic scission of an ether linkage and that the ethanamine chain in α-methylmorphimethine was therefore linked to the phenanthrene nucleus through oxygen (1). Morphine, in which the nitrogen ring is still intact was represented as containing an oxazine ring:

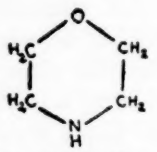


III. Methylmorphimethine (1889)



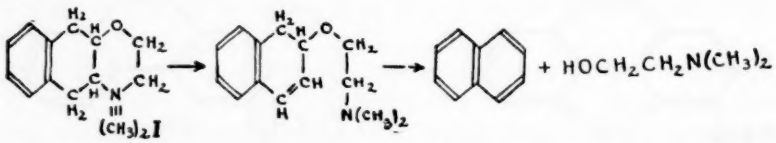
IV. Morphine (1889) (1)

This theory of the structure of morphine led to the synthesis of a large number of so-called morpholines, derivatives of the parent substance morpholine V (3) (4),

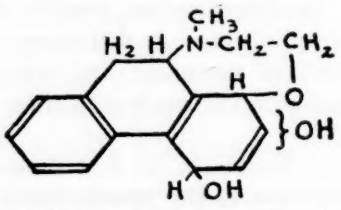


V. Morpholine

which was so named because of its supposed relationship to morphine. Naphthalanmorpholine in particular proved to be a strong, alkaloidlike base, which underwent degradation by the Hofmann method with loss of ethanoldimethylamine.



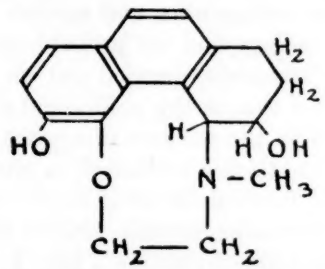
The extraordinary ease with which the last stage of this degradation takes place, in contrast with the difficulty with which methylmorphimethine breaks down, made an ortho attachment of the nitrogen chain on the hydroaromatic ring in morphine improbable, and led Knorr to advance the modified oxazine formula (5).



VI Morphine (Knorr 1899) (5)

The determination of the structure of methylmorphol (p. 283) and thebaol (p. 294) made certain the position of two of the oxygen atoms in morphine, and of all three in thebaine. With the recognition of the relationship between thebaine and codeinone (6) (7) (p. 247), and conversion of the latter to methyl-

thebaol (3, 4, 6-trimethoxyphenanthrene), the location of all of the oxygen atoms in morphine was accomplished. Whether the nitrogen chain was attached through oxygen to the nucleus remained still in question. The peri-ring structure of VI was in any case untenable, and the oxazine formula was again altered to represent morphine as a meso-morpholine of phenanthrene (6) (VII).[9]

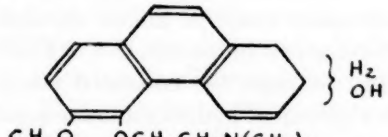


VII Morphine (Knorr, 1903)

This formula admittedly left several facts unexplained, especially the existence of the isomeric methylmorphimethines (6) (8).

It was further found that methylmorphimethine or the methiodides of thebaine or codeinone under special conditions (p. 285) could be split to phenanthrene derivatives and dimethylaminoethyl ethyl ether (9) (10). It seemed excluded that this ether resulted from a primarily formed ethanoldimethylamine, which does not etherify under the experimental conditions imposed, and there remained only the assumption that the side chain split out as a hypothetical vinyldimethylamine, $(CH_3)_2N–CH=CH_2$, which in the nascent state added a molecule of alcohol to give the ether. This hypothesis likewise explained the appearance of dimethylaminoethyl acetate in acetolytic degradation of morphine derivatives, by postulating addition of acetic acid to the vinylamine (10). The formation of tetramethylethylenediamine in the alkaline degradation of thebaine methiodide (11) was believed to be due to combination of the vinyl compound with dimethylamine, which is always present in small amounts in these degradations (10).[10] Experimental proof of this hypothesis could not be obtained, since all attempts to prepare vinyldimethylamine failed (14). Nevertheless, the conception that ethanoldimethylamine is not a primary product of methylmorphimethine degradation removed the chief support for the hypothesis that the amino alcohol arose from a hydrolytic scission of the ether linkage postulated in the oxazine formula.

Further studies soon yielded additional evidence against the oxazine hypothesis. The methylmorphimethine derived from a mesomorpholine type (VII) would be represented as in VIII:



VIII

IX

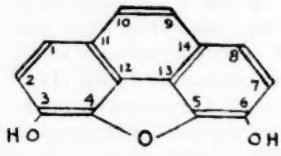
[9] *Cf.* the Vongerichten formula of 1900, p. 343.

[10] Tetramethylethylenediamine is also observed as the basic product when α-methylmorphimethine is decomposed with hydrogen chloride at 180° (12); in this case Knorr was able to show that chloroethyldimethylamine, which is probably the primary product of the reaction, polymerizes to N-dimethylpiperazine dimethochloride, which is converted by alkali to tetramethylethylenediamine, acetylene, and ethanoldimethylamine (13).

A methylmorphimethine so constituted should lose water easily to go to a completely aromatic system, a change which can not be realized experimentally (8). Moreover, the synthetic base IX differs from methylmorphimethine considerably in the ease with which it is split by hydrogen chloride or acetic anhydride, and, in contrast to methylmorphimethine, is stable toward sodium ethylate at 150° (8).

Up to this point the evidence for and against the oxazine formula has rested largely on analogy and the probable behavior of the structures involved. The researches carried out on thebainone in 1905 resulted in definite proof that in this compound the ethanamine chain could not be attached to the nucleus through oxygen. Thebainone (p. 308), $C_{18}H_{21}O_3N$, contains a methoxyl, a phenolic hydroxyl, and a keto group (15); the function of all of the oxygen atoms is known. Acetolysis of methylthebainonemethine yielded dimethylmorphol and the acetate of ethanoldimethylamine (16); i. e., the same basic product as is obtained in the degradation of methylmorphimethine, thebaine, or codeinone. The fact that methylthebainonemethine could be split to yield ethanoldimethylamine showed that the formation of the latter is not necessarily due to hydrolytic scission of an ether linkage, but could result from breakage of a carbon-to-carbon bond. This observation removed the last support of the oxazine hypothesis (8) (16).

The results of the degradation of thebainone, which led to the abandonment of the oxazine hypothesis, and the proved constitution of morphenol, brought Knorr and Pschorr (16) to the conclusion that the three morphine alkaloids are derivatives of 3, 6-dihydroxyphenanthrylene oxide, (X),

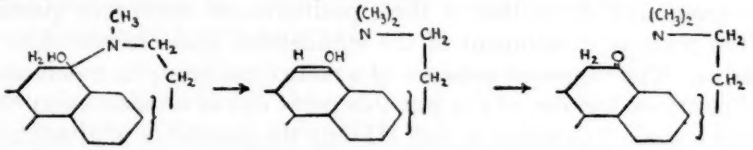


X

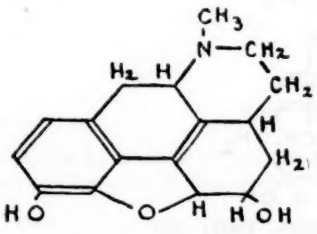
in which an ethanamine chain $-CH_2CH_2NCH_3-$ is attached to a partially reduced aromatic ring.

Through degradation of hydroxycodeine, Knorr (17) (18) was able to show that in this base the ethanamine chain is linked through nitrogen to one of the hydrogenated bridge carbon atoms, C-9 or C-10. Knorr's proof, which is given in detail on page 180 consisted essentially in showing that the new hydroxyl group of hydroxycodeine must be on C-9 or C-10, since the methoxydiacetoxyphenanthrene resulting from acetolysis of hydroxycodeinemethine can be oxidized to a phenanthrenequinone type only with loss of an acetoxy group. Furthermore, the hydroxyl group in question functions as an alcohol, whence it follows that the 9, 10-bridge is hydrogenated. The abovementioned hydroxycodeinemethine contains a keto group, and but

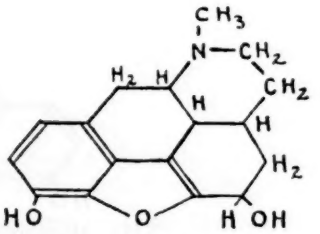
one alcoholic hydroxyl; the second hydroxyl in hydroxycodeine must be located on a carbon atom which becomes doubly linked when the nitrogen ring opens, i. e., the nitrogen ring must be attached to C-9 or C-10.[10]



PYRIDINE FORMULA.—The location of the nitrogen linkage of the ethanamine chain on the bridge carbon atom led Knorr (18) to put forward a modification of the Pschorr (21) pyridine formula of 1902. Reasoning from the proved presence of a hydrogenated pyridine ring in apomorphine (p. 262), Pschorr had evolved for morphine the structure XI (21) (22) (23) (24) (15).



XI. Morphine (Pschorr, 1902)



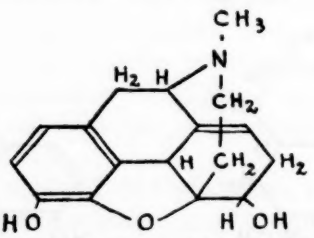
XII. Morphine (Knorr, 1907)

If the Pschorr formula (XI) were correct, the methine base from hydroxycodeine should show the phenolic character to be expected of an α- or β-naphthol derivative, which it does not do (25). This fact led Knorr to modify the Pschorr formula as in XII (18). One of the chief advantages seen in the "pyridine formula" was that it placed morphine in close relationship to papaverine, narcotine, laudanosine and the other isoquinoline opium alkaloids (26), a connection which later formulas have also sought to establish. (See p. 352.)

A study of the isomeric codeines soon caused Knorr to abandon the hypothesis of an ethanamine linkage to C-8 (26). Morphine and codeine exist in four isomeric forms (p. 209) in which the fundamental carbon-nitrogen skeleton is unchanged; all of the isomeric codeines may be converted through the chlorocodides to the same desoxycodeine (p. 235). Codeine and isocodeine oxidize with conversion of the secondary alcoholic group to a ketone group (27), giving codeinone (p. 247), in which the keto group lies in position 6, as is shown by degradation to 3, 4, 6-trimethoxyphenanthrene (6) (10). Pseudo-

[10] The Emde degradation of codeine methyl ether methochloride yields the same α-methylmorphimethine methyl ether as does degradation by the usual Hofmann method (19), a fact which Schöpf has construed as proof that nitrogen is attached to C-9 (20).

codeine and allopseudocodeine, on the other hand, give on oxidation an isomeric ketone, pseudocodeinone, in which the keto group is at C-8 (26) (28).[11] Codeine and isocodeine therefore have a secondary alcoholic group at C-6, pseudocodeine and allopseudocodeine have this group at C-8; neither of these positions can come into question as the point of attachment of the ethanamine chain in morphine or codeine. The supposed presence of a methylene group in codeinone [12] and pseudocodeinone, at C-7 put this point out of consideration (26). There remained therefore in ring III only the possibility of attachment at C-13, C-14, or C-5.[13] The first two were regarded as excluded on the grounds that in the completely aromatic thebenine the ethanamine chain is still attached to ring III (26).[14] Reasoning from the considerations given above, Knorr and Hörlein advanced (1907) the following morphine formula, which dominated for nearly 20 years the theory of morphine structure:



XIII. Morphine (Knorr-Hörlein, 1907) (26)

In favor of linking the N- to C-9, was cited the mechanism for apomorphine formation. The double linkage at C-8-C-14 was justified by the ketonic character of the methine base from hydroxycodeine, and the apparent presence of a methylene group at C-7 in codeinone. The isomerism of α- and β-, or γ- and δ-methylmorphimethines was explained by a shift of the double linkage into ring II, at C-13-C-14. In codeine the 7-membered heterocyclic ring is under but slight strain, in thebaine, where another double linkage is present, the strain is much greater, which is in accord with the relative instability of thebaine.

With complete aromatization of ring III, as in thebenine, apomorphine, or morphothebaine, the nitrogen ring must break (thebenine) or shift to a more favorable position (apomorphine, morphothebaine) (26). The position assigned to the hydroaromatic double linkage in the Knorr formula is not in accord with the behavior of codeine with cyanogen bromide (Von Braun (32)), and results

[11] Through experiments carried out on brominated codeine- and pseudocodeine-methyl ethers, Pschorr (29) showed that the shift of the hydroxyl actually took place in the change from codeine to pseudocodeine and not at some later stage of the degradation, a point of vital importance in deciding against the pyridine formula.

[12] It is now very doubtful whether this statement in regard to codeinone is true. (*Cf.* p. 248.) In dihydrocodeinone, however, it can be shown (30) that a methylene group is adjacent to the carbonyl group, i. e., at C-7.

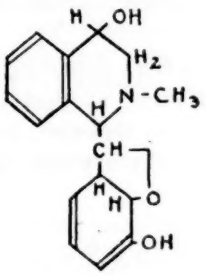
[13] Faltis (31) (1906), in some theoretical speculations on the origin of alkaloids in the plant depicted morphine and thebaine with an ethanamine chain linked to C-9 and C-5 as in the Knorr formula. The unsaturation in morphine was located at C-13 and C-14; thebaine was represented as containing a quinoid grouping (unsaturation at C-13 - C-14 and C-6 - C-7), the tendency of which to become aromatic was supposed to account for the relative instability of thebaine.

[14] The contingency that thebenine might be formed by a shift of the chain from some other position, a mechanism which was accepted to account for apomorphine and morphothebaine, was not considered.

in a β-methylmorphimethine formula which is in disagreement with hydrogenation experiments (33) (p. 347). The arguments which resulted in locating the unsaturation at another point in later formulas are given on page 349.

Before the most recent developments in the theory of morphine structure are presented, other proposals which have appeared in the literature will be briefly reviewed.

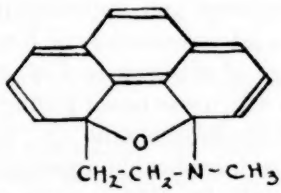
VIS FORMULA (34).—This extraordinary formulation, which represented morphine as a benzylisoquinoline derivative, was put forward on the unsupported assertion that the phenanthrene nucleus is not present in morphine, but is formed by a complex rearrangement of the benzylisoquinoline structure during degradation.[15]



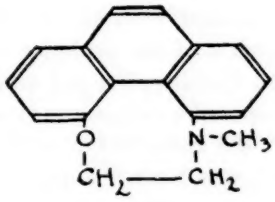
XIV. Morphine (Vis, 1893)

The Vis formula is entirely inadequate to explain the complex changes and relationships of morphine, and was critically disposed of by Knorr (35).

VONGERICHTEN FORMULA.—Basing his speculations largely upon observations made during a study of the morphenol degradation (p. 282) of the morphine alkaloids, Vongerichten (36) made two tentative structural proposals in 1900, in which no conjecture was made as to the location of the alcoholic hydroxyl group or the saturated portion of the nucleus.



XV. Morphine (Vongerichten, 1900)

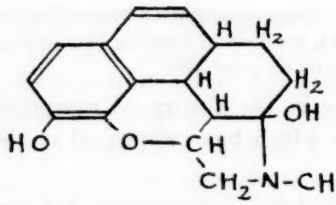


XVI

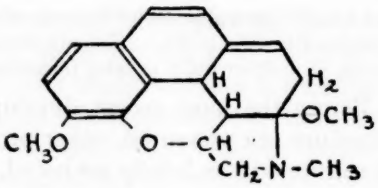
The formulas are unsupported by other evidence, and are obviously open to very numerous objections.

BUCHERER FORMULA.—Through an extension to morphine of his investigations on sulphurous esters of pyridine bases, Bucherer (37) arrived at the following formulas for morphine and thebaine (38).

[15] The centric arrangement of unsaturated linkages used by Vis is here shown in the more usual way as double linkages.



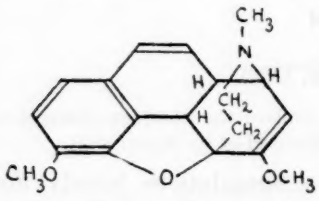
XVII. Morphine (Bucherer, 1907)



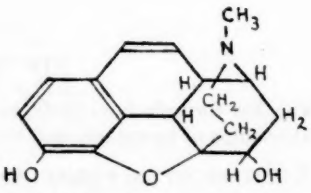
XVIII. Thebaine (Bucherer, 1907)

These formulas, which were believed to account for apomorphine and morphothebaine formation, for the phenyldihydrothebaine reaction, and others, obviously suffer from most of the disadvantages of the old oxazine formula.

FREUND FORMULA.—In radical departure from the oxazine hypothesis which was in general favor at that time (1905), Freund (39), as a result of his researches on thebaine, advanced a phenanthrylene oxide formula for thebaine and morphine (compare the earlier oxazine formula of Freund) (11).

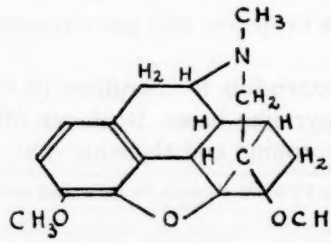


XIX. Thebaine (Freund, 1905)

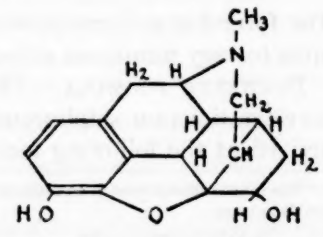


XX. Morphine (Freund, 1905)

With this formula it was possible to explain in a satisfactory way the conversion of thebaine through thebenine and thebenol to pyrene, but the mode of linkage of the ethanamine chain is in contradiction with the later work on the degradation of hydroxycodeine, and can not be reconciled with the structure of morphothebaine and apomorphine. In view of the evidence which was found in later researches of Knorr and Pschorr, Freund abandoned the linkage of nitrogen to C-8, and proposed a camphane type of structure (40) which was based primarily on the remarkable indifference of phenyldihydrothebaine (p. 332) and was further supported by the otherwise inexplicable appearance of two isomeric tetrahydrodesoxycodeines (41) (p. 240).



XXI. Thebaine (Freund, 1916)

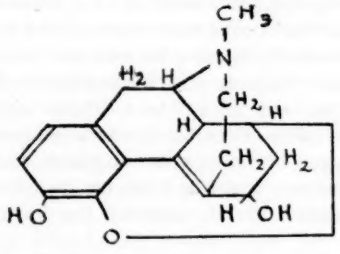


XXII. Morphine (Freund, 1916)

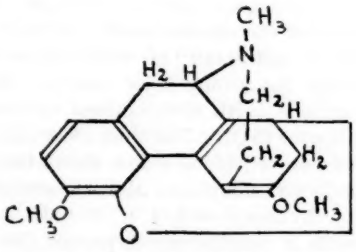
The camphane formula lent itself remarkably well to the explanation of the complicated phenomena in morphine chemistry, in particular to the mechanism of formation of apomorphine, morphothebaine, and thebenine (40) (42) and reappeared in later theoretical speculations in modified forms (42) (43). Against the camphane formula may be advanced the results of ozonolysis of thebaine, whereby the methyl ester of an aldehyde acid, thebaizone (p. 296) is obtained (23) (44); thebaine behaves as though it contained a double linkage at C-6-C-7. Dihydrothebaine likewise shows the presence of this double linkage, for it has the character of an enol ether, and saponifies readily to dihydrocodeinone (45) (p. 248). Codeine, moreover, is markedly unsaturated toward permanganate (42) (46) (47) (48), and both codeine and morphine hydrogenate in the presence of platinum or palladium with the greatest ease (49) (50). The hydrogenation process with thebaine is more complicated, but an addition of 4 hydrogen atoms catalytically to yield tetrahydromorphine dimethyl ether is possible (20).[16]

The supposed existence of isomeric tetrahydrodesoxycodeines which constituted such a striking confirmation of the camphane formula and exerted a strong influence later on similar formulas, was founded on erroneous experimental results (51). Only one tetrahydrodesoxycodeine exists (p. 238), and all of the relationships in the desoxycodeine series can be adequately explained on the basis of the Knorr or similar formulas.

FALTIS FORMULA.—Reasoning that the weakness of existing morphine formulas lay in their inability to explain satisfactorily the tendency seen in so many reactions for a hydroxyl group to appear on C-8, Faltis (46) (52) (1917) constructed a formula which should account for this fact. The novel feature consisted in linking the indifferent ether oxygen from C-4 to C-8.



XXIII Morphine (Faltis, 1917)



XXIV Thebaine (Faltis, 1917)

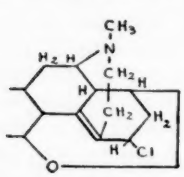
The double linkages in thebaine and morphine were arranged to correspond with Von Braun's (32) observation that these two bases behave toward cyanogen bromide as though they contained a double bond in the β, γ-and γ, δ-positions, respectively. (See p. 347.)

The 4, 8-bridge was regarded as a strained structure in morphine and codeine; the presence of another double bond in thebaine was considered to increase this strain, thus explaining the relative instability of thebaine.

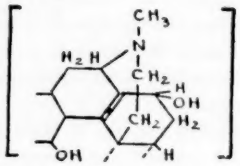
The Faltis theory accounts readily for the hydroxyl on C-8 in thebenine as due to a hydrolytic scission. In morphothebaine also it is apparent that a shift of the ethanamine chain onto C-8 could result in opening the ether bridge with formation of a phenolic hydroxyl on C-4. Difficulties appear in accounting for the hydrolysis of the halogenocodides. Chlorocodide is assumed to hydrolyze with a breakage of the strained ether ring and a 1, 4-elimination of hydrochloric

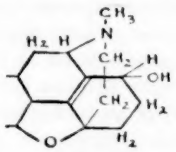
[16] Other facts which speak against the Freund formula are cited by Von Braun (Ann. **451,** 59 (1927)) and Wieland (Ann. **444,** 69 (1925)).

acid from C-6 and C-14. The newly formed phenolic hydroxyl is then conceived as adding to a free valence on C-5, closing the 4, 5-ether bridge and yielding pseudocodeine of the Knorr formula.



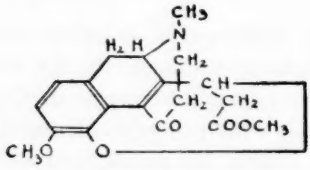
XXV



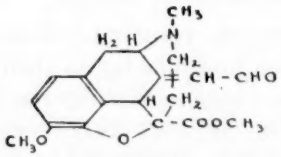


XXVI

Pseudocodeine can, however, be converted back to chlorocodide or bromocodide, whereby the strained 4, 8-ring is again set up from the stable 4, 5-bridge (XXVI ——→XXV). Among numerous other substances which offer difficulty of explanation by the Faltis hypothesis may be mentioned thebaizone (23), the ozonolysis product from thebaine (see p. 296), which according to the Faltis conception must be a ketone XXVII, according to the Knorr theory an aldehyde XXVIII.



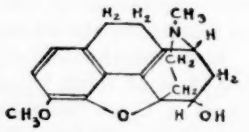
XXVII



XXVIII

From the negative results obtained with the Angeli-Rimini reaction on a minute amount of thebaizone, Faltis (53) concluded that thebaizone was not an aldehyde. Wieland and Small (44) were able to show the aldehyde-ester formula as valid, through the strong color reaction with Schiff's reagent, and by oxidation of thebaizone (with simultaneous hydrolysis of the ester group) to a dibasic acid (*cf.* Speyer (54)). The work of Schöpf (p. 249) on the Beckmann rearrangement of dihydrocodeinone oxime shows that the oxygen bridge in this substance, and therefore in morphine, already occupies the position which it is known to have in methylmorphenol, i. e., it links carbon atoms 4 and 5, whereby the Faltis formula is conclusively disproved (20).

GADAMER FORMULA.—The observed seasonal conversion of thebaine into isothebaine (55) (56) (an apomorphine type) in *Papaver orientale* was construed by Gadamer as an indirect process which could not be well accounted for by a thebaine formula having the ethanamine chain linked at C-9. Gadamer therefore proposed the modified Freund formula XXIX.

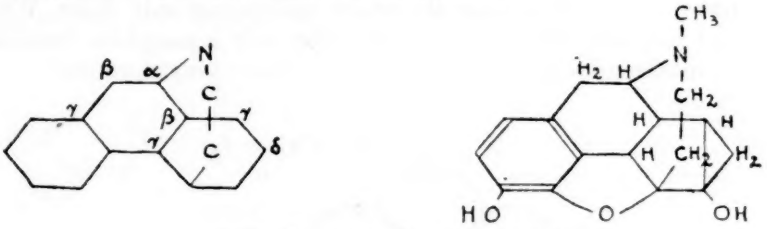


XXIX. Codeine (Gadamer, 1913)

The formula has no experimental basis, and is open to the same objections as that of Freund (XX). Apomorphine formation was

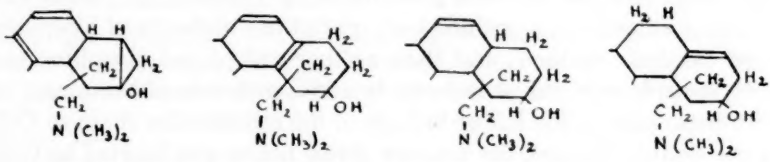
postulated as perhaps taking place through an intermediate substance having the Knorr formula.

VON BRAUN FORMULA.—The fact that morphine and codeine, in contrast to thebaine, react with cyanogen bromide with replacement of the N-methyl group by CN, but with no scission of the nitrogen ring, brought Von Braun (32) to the conclusion that in these two alkaloids there could be no double bond in the β, γ-position to nitrogen i. e. in neither the 8, 14- (Knorr formula) nor 13, 14-positions. Since evidence in the codeinone series (26) was believed to preclude the presence of a double bond in the γ-δ-position, C-7-C-8,[17] Von Braun's investigation found expression in the formula:



XXX. Morphine (Von Braun 1914)

Thebaine, in which by the Knorr formula a double bond lies β, γ-to nitrogen, suffers ring scission with cyanogen bromide, but tetrahydrothebaine (so called), where the β, γ-unsaturation has been eliminated, behaves like morphine and codeine. The Von Braun researches raised the first evidence against the 8, 14-location of the double linkage as found in the Knorr formula. Formula XXX explains the impossibility of splitting out smoothly hydrochloric acid from chloromorphide, the difficulty of addition of two bromine atoms to morphine or codeine, and the transition from the codeine to the pseudocodeine series. Difficulties appear in accounting for the isomeric methylmorphimethines (32), and for the formation of codeinone by oxidation of codeine (42). While an explanation for the latter process may be devised (57), the strongest evidence against XXX, as was pointed out by Von Braun (57), lies in the conversion of codeinone back to codeine. Researches on the hydrogenation of the isomeric methylmorphimethines (p. 271) finally caused Von Braun to reject the bridge formula. α- and β-Methylmorphimethines, which would be represented by XXXI and XXXII, respectively,



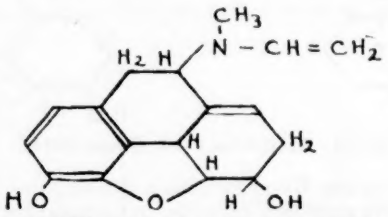
XXXI XXXII XXXIII XXXIV

according to the Von Braun theory, hydrogenate with addition of 4 hydrogen atoms to give the same tetrahydro product. When XXXI is partially hydrogenated, addition of two atoms of hydrogen to the double bond would be expected, whereas in XXXII, which is a naphthalene derivative, a mixture of tetrahydro-

[17] This point is still not satisfactorily settled; see for example Gulland and Robinson, J. Chem. Soc. **123**, 1001 (1923); Wieland, Ann. **444**, 82 (1925); Schöpf, Ann. **452**, 212 (note 2) (1927); **458**, 161 (1927).

methylmorphimethine and of unchanged XXXII should be obtained. Experiment yielded quite different results. From α-methylmorphimethine the dihydromethylmorphimethine XXXIII resulted, which was already known as a degradation product of dihydrocodeine, whereas from β-methylmorphimethine an isomeric dihydromethylmorphimethine was obtained, in which the 9, 10-double linkage must be saturated. (See p. 272.) This product can not be derived from XXXII, and is best depicted by XXXIV. These results are not in agreement with the known inactivity of a 3-membered ring in comparison to a double linkage (58), and led Von Braun (57) to adopt the Wieland and Robinson convention of a double linkage at C-7-C-8.

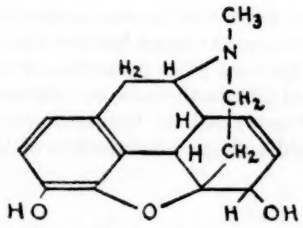
WIELAND FORMULA.—In an attempt to account for the extraordinary ease with which many compounds in the morphine series, as codeinone and thebaine, lose the entire ethanamine side chain, Wieland and Kappelmeier (59) proposed tentatively a morphine formula which contained no nitrogen ring, the so-called "vinyl formula":



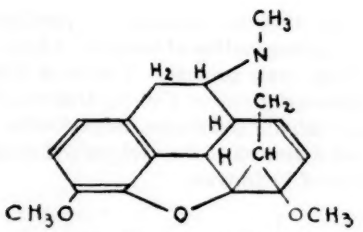
XXXV. Morphine (Wieland 1911)

The vinyl formula was unsupported by direct experimental evidence. It was argued that it explained the surprising ease of ammonia formation observed in gentle oxidations of morphine, as well as the firmly attached "hydrate water" of morphine and codeine, which was conceived to be water of constitution added at the vinyl group. As a further advantage, it made unnecessary the assumption of a most unusual type of ring structure. While the results of the Hofmann degradation point plainly to the presence of a nitrogen ring in morphine, the assumption was here made that the carbon-to-carbon linkage of the side chain existing in methylmorphimethine was formed by a secondary reaction of the extremely reactive vinyl group, an explanation which was also used to account for thebenine and for the proved ring structure in apomorphine and morphothebaine.

The vinyl formula was soon abandoned by Wieland (60), for it was found that anhydrous morphine took up but one molecule of hydrogen by the catalytic method, and that neither anhydrous morphine nor diacetylmorphine could be induced to add a molecule of bromine. A return was made to the Knorr linkage of the ethanamine chain to C-5, but the double linkage, for reasons given below was located at C-7-C-8, while for thebaine, which at that time had been brought to take up but one molecule of hydrogen, a bridge-linkage of the Freund type was postulated (42) (61):

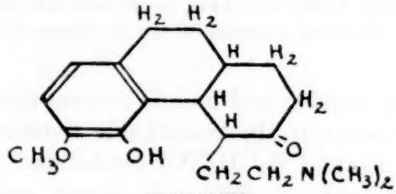


XXXVI. Morphine (Wieland 1925)

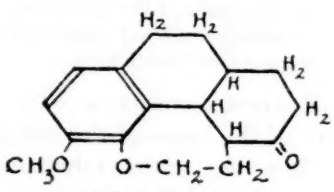


XXXVII. Thebaine (Wieland 1925)

The argument advanced for locating the side chain on C-5 was based on the behavior of the ketone XXXVIII, in which the original position of the side chain is preserved, since it is prepared from tetrahydromethylmorphimethine or from dihydrothebaine by methods which could not cause a shift.



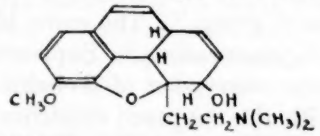
XXXVIII



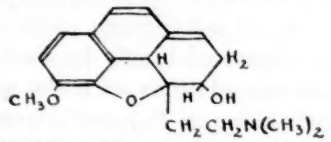
XXXIX. Thebenone

The ketone could be degraded to an ether type, thebenone (XXXIX), showing that the side chain must be in a position favorable for ring closure with the phenolic hydroxyl at C-4 (i. e., must be on C-13 or C-5). The ketone XXXVIII yielded, however, only *one* condensation product with benzaldehyde or piperonal, as did thebenone. If the side chain is attached to C-13, the presence of two active methylene groups adjacent to the carbonyl should result in formation of two condensation products. (*Cf.* however, Schöpf (20).)

Placing the double linkage in the new position at C-7 - C-8 [18] clarified the relationship of the isomeric methylmorphimethines; the change from α-methylmorphimethine to β-methylmorphimethine (p. 274) consists solely of a shift of the double linkage to a position of conjugation, from C-7 - C-8 to C-8 - C-14.

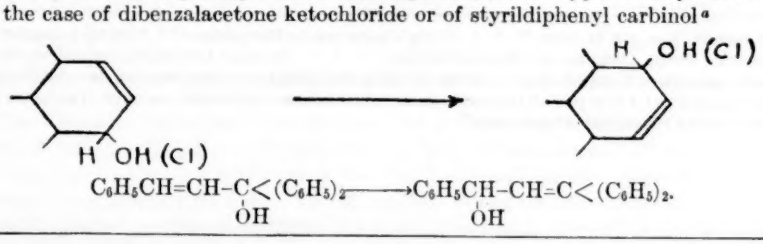


XXXX. α-Methylmorphimethine



XXXXI. β-Methylmorphimethine

It further brought the codeine-pseudocodeine relationship into analogy with known processes, depicting it as a rearrangement of the type already observed in the case of dibenzalacetone ketochloride or of styrildiphenyl carbinol [a]

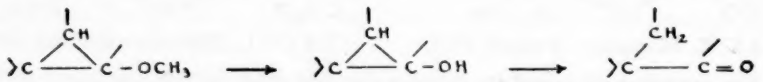


$$C_6H_5CH{=}CH{-}C{<}\overset{OH}{(C_6H_5)_2} \longrightarrow C_6H_5CH{-}CH{=}C{<}\overset{OH}{(C_6H_5)_2}.$$

[18] The same formula modification in this respect was introduced independently by Gulland and Robinson at the same time.

[a] Strauss and Ehrenstein, Ann. **442**, 93 (1925); Ziegler, Ann. **443**, 161 (1925).

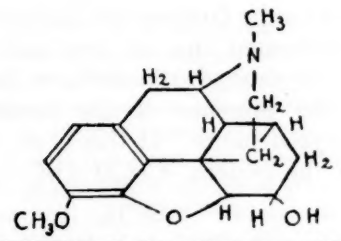
The thebaine formula was justified through the facts then known concerning the hydrogenation of thebaine, which ordinarily behaves as though but one double linkage were present. The most difficult point, the enol ether properties of the methoxyl group on C-6 (hydrolysis of thebaine and dihydrothebaine to codeinone and dihydrocodeinone, respectively, p. 247) was explained by the assumption that a system of the cyclopropyl alcohol type could undergo isomerization at the time of hydrolysis.



Among other facts which are difficult of explanation on the basis of the 3-membered ring formula may be mentioned the ozonolysis of thebaine, which proceeds in complete accord with the presence of a double linkage at C-6 - C-7. Wieland's study of the ozonolysis product, thebaizone (44), convinced him that its formation was best explained by a thebaine formula of the Robinson type containing two double bonds.

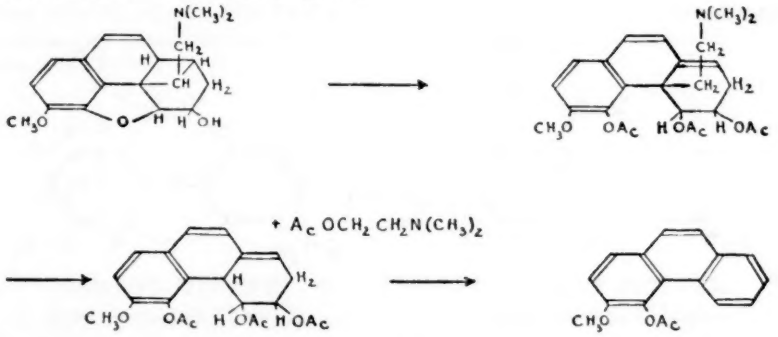
ROBINSON FORMULA.—The most striking and unique general property of the bases of the morphine series is the remarkable tendency to lose the entire ethanamine chain $-CH_2CH_2NCH_3-$exhibited in many degradative processes (see table, p. 285). It seems quite certain that this characteristic decomposition must have its origin in some peculiarity in the morphine molecule, and any acceptable structural formula should be capable of showing a cause for the degradation. From a consideration of this fact, Gulland and Robinson (43) arrived at the following conclusion: "The driving force behind the change is doubtless the tendency to produce an aromatic nucleus, because the extrusion of the side-chain is never observed independently of the formation of the true phenanthrene derivative. The formation of the aromatic phenanthrene derivative can not take place for structural reasons unless the ethanamine side-chain is displaced in favour of a hydrogen atom or a hydroxyl group." The same idea was expressed briefly by Pschorr some 13 years earlier.[19] Supporting their speculations with the phytochemical conversion of thebaine to isothebaine in *Papaver orientale*, and with the supposed existence of two isomeric tetrahydrodesoxycodeines (see p. 240) these authors set up a modified Freund camphane formula which also embodied the principle of the Pschorr pyridine formula:

[19] Pschorr, Ann. 373, 64 (1910), " • • • die Wanderung des Komplexes –C·C·N, sowie besonders sein beispiellos leichte Ablösung vom Phenanthrenkern • • • bei einer Abzweigung der Seitenkette von einem *quaternaren* Kohlenstoffatom (13 oder 14) darin ihre Erklärung finden würden, dass der Übergang der Benzolkerns III vom partiell hydrierten in den rein aromatischen Zustand nur unter Wanderung bzw. Ablösung der Seitenkette erfolgen kann."



XXXXII. Codeine (Robinson 1923)

The formation of acetylmethylmorphol by acetolysis of methylmorphimethine may be used as an illustration of the compulsory removal of the side chain to permit formation of the aromatic system:

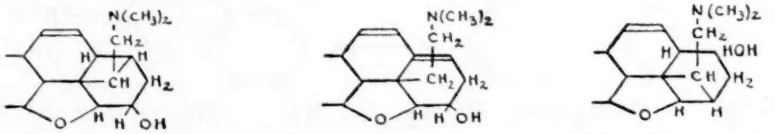


The camphanelike formula represented the codeine-pseudocodeine change as of the geraniol-linalool type,

$$(CH_3)_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}C(CH_3){:}CH{\cdot}CH_2OH$$
$$\Updownarrow$$
$$(CH_3)_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}C(CH_3)OH{\cdot}CH{:}CH_2$$

a comparison which nevertheless involved the strained assumption of a peculiar intermediate substance.

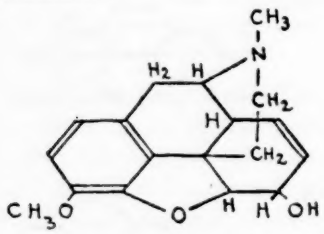
The isomerism in the methylmorphimethine series offers no difficulty of explanation. α-Methylmorphimethine is regarded as still containing the bridge bond, which breaks under the influence of alkali to give an ethylenic bond conjugated with that in the 9, 10-position. In the case of ϵ-, and ζ-methylmorphimethines the possibility of conjugation is eliminated, so that there is no reason to expect these methine bases to isomerize.



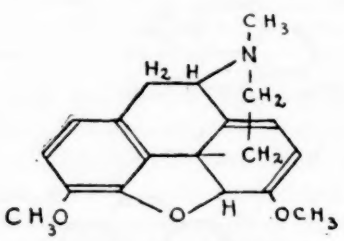
α-Methylmorphimethine β-Methylmorphimethine ϵ- or ζ-Methylmorphimethine

The Robinson camphane formula like that of Freund is excellently adapted to account for the conversion of codeinone to morphothebaine and of morphine to apomorphine, since the breakage of the 13, 15-linkage results immediately in a nitrogen ring located on C-8. The formation of thebenine, where the nitrogen chain is located on C-5 necessitates the assumption of a shift of the entire chain, or of a remarkable fission of four rings and wandering of the side chain, followed by ring closure. Thebaine was regarded as containing one ethylenic bond or another easily broken bridge bond.

Experiments carried out by Gulland and Robinson (47) on hydroxycodeinone (p. 255) indicated that it does not contain the group $-CO-CH_2-$ but that dihydrohydroxycodeinone does, facts which are best explained by the presence of the arrangement $-CO-CH=C-C(OH)-$ in hydroxycodeinone. If this is so, it follows that thebaine would contain the system $-C(OCH_3)=CH-C=C-$ and not the bridge linkage previously proposed. This is in better accord with the ease of hydrogenation of codeine, and its addition of two hydroxyl groups with permanganate (48) in the manner of a substance containing an ethylenic bond. Codeine and thebaine were therefore assigned the formulas:



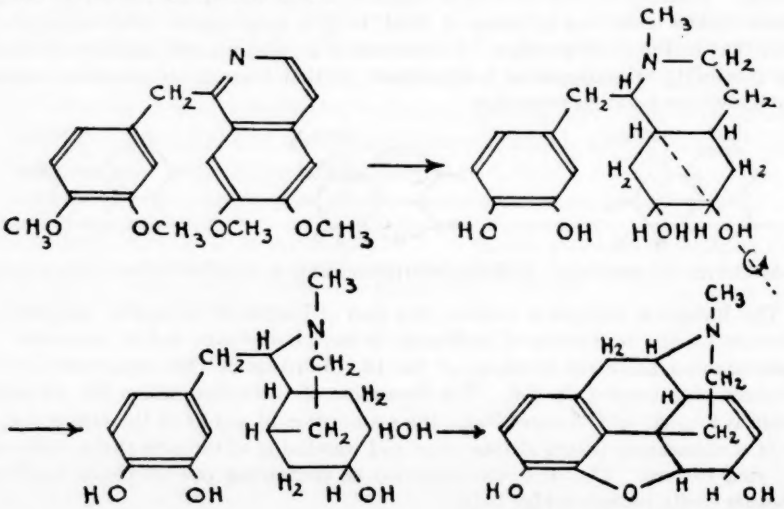
XXXXIII. Codeine
(Gulland-Robinson, 1925)



XXXXIV. Thebaine
(Gulland-Robinson, 1925)

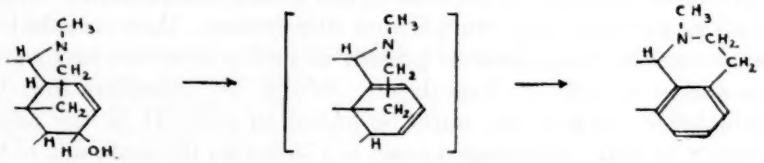
With the adoption of these formulas it became necessary to explain the supposed isomerism of the tetrahydrodesoxycodeines on a stereochemical basis (spatial arrangement of the hydrogen atom on C-14), an assumption which is superfluous in view of the later researches of Small and Cohen (51). Whether other known cases of isomerism require this explanation is not certain.

The formula of Gulland and Robinson permits the establishment of a hypothetical formal relationship between alkaloids of the papaverine type and morphine, a conception which may be used to account for the formation of the two types of alkaloid in the plant (20) (47):



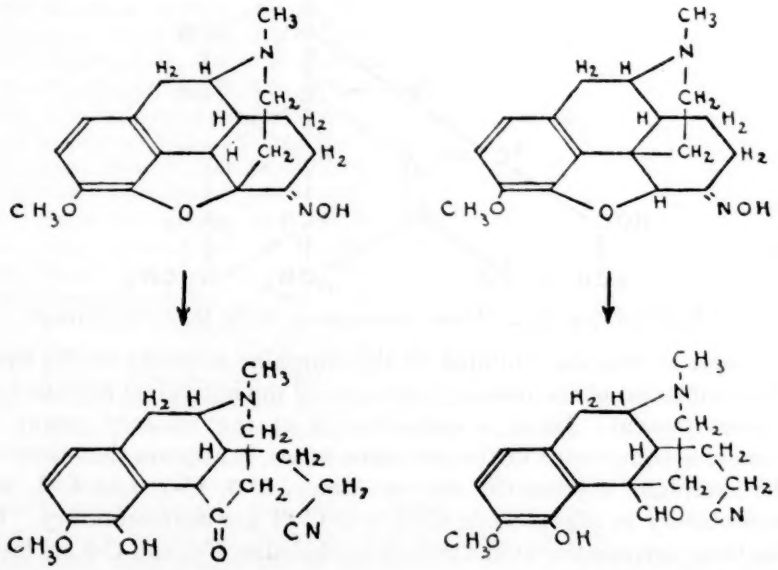
Formula XXXXIII possesses a decided advantage over the older camphane formula in making the codeine-pseudocodeine rearrangement strictly analogous to the geraniol-linalool type of change.

According to the experiments and speculations of Schöpf (62), the Robinson formula is capable of explaining in a reasonable way the remarkable changes of thebaine or codeinone to morphothebaine, and of morphine to apomorphine. The first-mentioned reaction is assumed to take place through hydrolysis of the enol ether group of thebaine, and addition of hydrogen chloride to the 8, 14-double linkage followed by a retropinacone rearrangement, whereby the ethanamine chain shifts from C-13 onto C-14. The tendency of ring III to become aromatic on heating with concentrated hydrochloric acid forces a further shift of the side chain from C-13 to C-8, resulting in morphothebaine (see p. 329). The formation of apomorphine (see p. 261) is similarly explained: the first step, loss of water from ring III of morphine results in two conjugated double linkages, and the tendency for aromatization is then strong enough to cause a shift of the side chain from C-13 to C-8.



The mechanism postulated for the formation of thebenine is given on page 323.

Schöpf (20) sought to obtain direct evidence for the location of the ethanamine chain by subjecting dihydrocodeinone oxime to a Beckmann rearrangement. If the Robinson formula XXXXIII is correct, the isoxime resulting must be an aldehyde XXXXV, whereas if the Knorr-Wieland formula (XXXVI) is correct a ketone XXXXVI must be obtained.



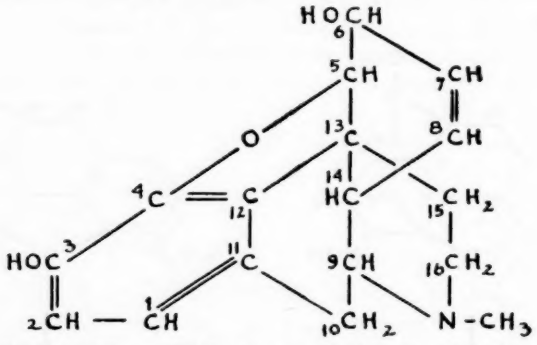
XXXXVI XXXXV

Neither the isoxime itself nor its methyl ether yielded the desired proof, and only after a long series of transformations could the conclusion be drawn that the isoxime must have an aldehyde structure as predicted by the Robinson formula.

It should be noted that the only evidence against the Robinson conception is of a negative nature, the failure of the above-mentioned thebenone (XXXIX) to condense twice with aldehydes (42). This evidence is, however, not necessarily binding, for other cases are known where only one of two methylene groups adjacent to a carbonyl is capable of condensing with aldehydes (20). Among other anomalies may be cited the apparent presence of an active methylene group in pseudocodeinone, and the extraordinary indifference of the ethylenic linkage in chlorocodide toward ozone (63). (See p. 212.)

Morphine and codeine contain no less than five asymmetric carbon atoms as part of a very complicated ring system. Any speculations concerning the configurations present in such a structure necessarily rest almost entirely on hypothesis. Schöpf (64) considers that the 5-membered oxygen ring must be linked to ring III in the cis-cis position, so that the hydrogen atom at C-5 lies on the same side of the plane of ring III as the nitrogen chain at C-13. Other speculations on configuration, as well as a space model illustration, are given in a later publication (65).

Emde (66) points out that the five asymmetric carbon atoms 6, 5, 13, 14, and 9 are linked consecutively in an unbranched carbon chain, as shown in Formula XXXXVII.



XXXXVII. Morphine. Emde Arrangement of the Robinson Formula

The optical rotation exhibited by the morphine molecule results from the summation of the rotatory moments of the individual asymmetric centers present. From a consideration of the rotatory power of numerous compounds in the morphine series, it appears that three of the morphine asymmetric carbon atoms, C-6, C-5, and C-9, are levorotatory in effect, while C-13 and C-14 are dextrorotatory. Of the three asymmetric atoms present in thebaine, C-5 and C-9 are levo, C-13 is dextrorotatory.

The formula of Gulland and Robinson, while as yet not proved beyond dispute, probably accounts best on the whole for the complicated facts of morphine chemistry, and until further more definite evidence is available may be accepted as representing the true structure of the morphine alkaloids.

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APPENDIX

To p. 11. Papaverine. Synthesis and pharmacodynamic action of a homoisopapaverine. Konek, Chem. Abstr. **25,** 3004 (1931). Technical manufacture of papaverine, ibid. **25,** 3005 (1931).

To p. 14. Tetrahydropapaverine. Späth and Berger, Ber. **63,** 2098 (1930). A synthesis of *d,l*-tetrahydropapaverine which is of interest from the phytochemical standpoint was accomplished by condensation of homoveratrylamine with homoveratric aldehyde in ether solution. Ring closure of the resulting Schiff's base type to *d,l*-tetrahydropapaverine took place on heating with 50% hydrochloric acid. The compound was characterized as the picrate, and as the acid oxalate. The latter shows the m. p. 204° to 205° (decomp.).

To p. 18. Papaverine. The increasing recognition of the therapeutic value of papaverine has resulted in a certain shortage of this drug. This has led to the preparation of substitutes, the most promising of which appears to be Eupaverine, 1-(3,4-methylenedioxybenzyl)-3-methyl-6,7-methylenedioxyisoquinoline. Eupaverine crystallizes as the hydrochloride with one molecule of water, $C_{19}H_{15}O_4N \cdot HCl \cdot H_2O$, m. p. unsharp at 158°. Cryst. from absol. alcohol it is anhydrous and m. at about 253° with decomp. The base is almost insoluble in water, sparingly sol. in ether, sol. in benzene or chloroform, and is best cryst. from methanol; m. p. 141°. Merck's Jahresbericht, **44,** 15 (Darmstadt, May, 1931).

To p. 18. Papaverine. Fleischer and Hirsch-Tabor, D. R.-P. 477577, Wagner's Jahresber. **75,** II, 178 (1929). Papaverine diethylbarbiturate cryst. from alcohol as a white powder of m. p. 138°.

To p. 32. Laudanosine. Bhagwhat, Moore and Pyman, J. Chem. Soc. **1931,** 433, have investigated the mechanism of the oxidation of laudanosine with manganese dioxide in sulphuric acid. The products are laudaline, veratraldehyde and $C_{14}H_8(OCH_3)_4$, colorless plates from acetone, m. p. 231° (*cf.* Pyman, J. Chem. Soc. **95,** 1266 (1909)). This proved to be 2,3,6,7-tetramethoxy-9,10-dihydroanthracene. Gadamer obtained the same substance from oxidation of laudanosine with mercuric acetate. The recognition of the true nature of this oxidation product invalidates Gadamer's theory of the formation of dimethoxybenzyl groups as an intermediate stage in this oxidation.

To p. 47. Narcotine. The estimation of narcotine in the presence of papaverine is accomplished by saponification of narcotine to narcotinic acid with standard alcoholic potassium hydroxide and titration of the excess of alkali. Snesarev, J. Chem. Ind. (Moscow) **8,** 161 (1931); Chem. Abstr. **25,** 4658 (1931).

To p. 63. Opianic acid. The cleavage of opianic acid and its esterification is discussed by Shorigin and coworkers, Ber. **64,** 274, 1631 (1931).

To p. 85. Narceine. Polonovski, Bull. soc. chim. (4) **49–50,** 542 (1931). Narceine is reduced in aqueous solution by sodium amalgam to $C_{28}H_{27}O_7N$, dihydronarceine. This is a secondary alcohol, formed by reduction of the narceine keto group. It loses water easily in boiling aqueous solution, or on long standing in the solid state, whereby a lactone ring is closed with formation of dihydronarcotinemethine. The last named product can likewise be prepared by alkaline reduction of aponarceine (p. 86) in alcohol. It is proposed to rename aponarceine "narcotimethine." Dihydronarcotinemethine is changed back to dihydronarceine by the action of hot alkali. By treatment with 30% hydrogen peroxide dihydronarcotinemethine is converted to an amine oxide, in contrast to aponarceine, which is transformed to narceine by this reagent. Dihydronarcotinemethine is esterified by alcohols in the presence of gaseous hydrogen chloride, with simultaneous substitution of the alcoholic hydroxyl by chlorine.

The analogous reactions have been carried out with nornarceine (p. 89), resulting in dihydronornarceine and the corresponding lactone, dihydronornarcotinemethine. When nornarceine is heated with an excess of acetic anhydride, lactone ring closure takes place, together with acetylation of the secondary amino group, resulting in acetylnornarcotinemethine, which can be saponified by alkali to acetylnornarceine.

DIHYDRONARCEINE: $C_{23}H_{29}O_8N$, soluble in chloroform, sparingly so in ether, m. p. 154° to 155°.

DIHYDRONARCOTINEMETHINE: $C_{23}H_{27}O_7N$, is not crystalline. —HYDROCHLORIDE, cryst. anhydrous, m. p. 200° to 210°. —NITRATE, cryst. from dil. alcohol, m. p. 196°, very slightly sol. in cold water. —TARTRATE, m. p. 140°. —PLATINICHLORIDE, yellow, sparingly sol. in water, m. p. 165°; after crystallization from alcohol it melts at 192°. —METHIODIDE, cryst. from acetone, m. p. 233° to 234°, sparingly sol. in cold water. DIHYDRONARCOTINEMETHINE-N-OXIDE, $C_{23}H_{27}O_8N$, cryst. from absol. alcohol, m. p. 153°.

CHLORODIHYDRONARCEINE METHYL ETHER is not cryst. but yields a HYDROCHLORIDE which cryst. from alcohol, m. p. 197°. CHLORODIHYDRONARCEINE ETHYL ETHER gives a HYDROCHLORIDE, $C_{25}H_{32}O_7NCl \cdot HCl$ of m. p. 199° to 200°.

ACETYLNORNARCOTINEMETHINE: $C_{24}H_{29}O_8N$, cryst. from absol. alcohol, m. p. 120°.

ACETYLNORNARCEINE, cryst. from absol. alcohol and ether as colorless prisms, m. p. 130°.

DIHYDRONORNARCEINE, white cryst. of m. p. 172°.

DIHYDRONORNARCOTINEMETHINE was obtained as the hydrochloride, cryst. from alcohol-acetone, m. p. 176°.

To p. 100. Cryptopine. Trier (Die Alkaloide, Vol. II, 494) states that the name cryptopine was derived from the conception of it as a "hidden," rare alkaloid.

To p. 138. Morphine. An account of Sertürner's life and reprints of his papers from Trommsdorff's Journal der Pharmazie and Gilbert's Annalen der Physik have recently been published in monograph form: "Friedrich Wilh. Sertürner, der Entdecker des Morphiums" by Franz Krömeke (Fischer, Jena 1925).

To p. 138. Morphine. An excellent account of the history and preparation of opium, and the separation of the alkaloids is given by Trier in "Die Alkaloide," Vol. II (Borntraeger, Berlin 1931). For a more detailed historical treatment of opium and culture of the opium poppy, see Jermstad, "Das Opium" (Hartleben, Vienna and Leipzig 1921). The extraction and purification of morphine on a laboratory scale and a complete description of factory procedure is given by Schwyzer, "Die Fabrikation der Alkaloide," p. 31 (Springer, Berlin 1927).

To p. 139. Morphine. Early investigators (Accarie, J. chim. méd. **1832,** 431; Jahresber. Chem. **4,** 250 (1834), Muerin, J. pharm. chim. **23,** 393 (1853)) claimed to have found morphine in poppy seeds. Later observers have found poppy seeds alkaloid-free (Sacc, Ann. chim. phys. **27,** 473 (1853), Clautriau, J. Pharm. **20,** 161 (1889), Mach, Landwirtschaftl. Versuchsstationen **57,** 419 (1902), Müller, Arch. Pharm. **252,** 280 (1914), Heiduschka, Schweiz. Apoth. Ztg. **57,** 447 (1919)). Seeds of the black poppy were found by Van Itallie and Toorenburg to contain traces of morphine and codeine (cited from Starkenstein). Chistoni (Chem. Abstr. **25,** 4084 (1931)) found no alkaloids in the seeds of var. album, but could isolate a substance (differing from morphine in action) which was toxic to white mice.

To p. 139. Morphine. In very early publications Petit (J. pharm. **1813,** 170) claimed that morphine was present in *Papaver orientale.* In addition to Dieterich, Tilloy (J. pharm. **1827**) and Selmi (Ber. **9,** 195 (1876)) claimed that morphine was present in *Papaver rhœas.* Riffard (J. pharm. **1830,** 547) and Meylink and Stratnik (Buchner's Repert. Pharmacie **36,** 143 (1831)), like Hesse, found no morphine in *Papaver rhœas.* Concerning *Argemone mexicana,* other investigators (Schlotterbeck, J. Am. Chem. Soc. **24,** 238 (1902), Schmidt, Arch. Pharm. **239,** 401 (1901), Le Prince, Bull. des Sciences pharmacol. **16,** 270 (1909)) were not able to confirm Charbonnier's find. In *Escholzia californica,* Danckwortt (Arch. Pharm. **228,** 572 (1890)), Wintgen (Dissert., Marburg 1898), Schmidt (Arch. pharm. **239,** 406 (1901)) and Fischer (Arch. Pharm. **239,** 421 (1901)) could find no morphine. Concerning the occurence of morphine in cultivated hops, see Chapman, J. Chem. Soc. **105,** 1895 (1904). (Cited from Starkenstein.)

To p. 140. Morphine, solubility—Guerin, J. pharm. Chim. **7,** 438 (1913), finds that at 15°, 100 g. of water dissolves 0.0288 g. of morphine. Marchionneschi, Chem. Zentr. **1907** II, 411, gives for ether

at 5°, 0.049%. Schäfer, Am. J. Pharm. **85,** 439 (1913), gives the solubilities: Ethyl alcohol 1:258, methyl alcohol 1:15, chloroform 1:2,500, benzol, 0, ethyl alcohol one part in chloroform four parts 1:150, ethyl alcohol one part in benzol four parts 1:500, methyl alcohol one part benzol four parts 1:40. Gori, Bull. de la chim. et pharmacol. **52,** 891 (1913), gives for carbon tetrachloride 0.025 parts in 100. Guerin (loc. cit.) found for dry acetone the solubility 1.28:100 at 15°, for 50% acetone-water, 1.32:1,000. M. Scholtz, Arch. Pharm. **250,** 418 (1912), gives: Aniline 6.5:100, pyridine 19:100, piperidine 66:100, diethylamine 8:100, all at 20°. (Cited from Starkenstein.) Anneler (Arch. Pharm. **250,** 193 (1912)) found the solubility 1:100,000 in benzol (Trier).

To p. 142. Morphine. The use of morphine, pseudomorphine, apomorphine, codeine, or papaverine as reagents for the detection of formaldehyde is described by Fulton, Ind. Eng. Chem., Analytical Edition **3,** 200 (1931). The Denigés-Oliver test for morphine has been examined critically by Bamford, Analyst **56,** 586 (1931), and extended as a colorimetric method for determining heroin. Ekkert, Pharm. Zentralhalle **71,** 550 (1930), describes the use of p-dimethylaminobenzaldehyde in conc. H_2SO_4 as a reagent for morphine, codeine, ethylmorphine, heroin or cryptopine (blood-red color). Eucodal, laudanon, narkofin, and parakodin give a red-brown color.

For an exhaustive examination of the methods in use for the determination of morphine up to 1920, see Jermstad, 'Monographie und Kritik der Methoden zur Bestimmung des Morphins im Opium," Dissertation, Basel 1920.

To p. 143. Morphine. An attempted synthesis of a tricyclic system of the type present in morphine is described by Manske, J. Am. Chem. Soc. **53,** 1104 (1931).

To p. 144. Morphine. Lesure, J. pharm. chim. **30,** 337 (1909), discusses the permanence of morphine solutions and the effect of sterilization in glass ampoules. The alkalinity of the glass causes precipitation of a considerable amount of the alkaloid from its salts. Addition of a little acid stabilizes the solutions. *Cf.* Droste, Pharm. Z. **58,** 737, 860 (1913), Mossler, Apoth. Ztg. **28,** 785 (1913); Z. allgem. oesterr. Apoth.-Ver. **51,** 489, 505, 537 (1913), Schäfer and Stich, Münch. med. Wochschr. **64,** 676 (1917). Partial decomposition of morphine under sterilization, Kollo, Bull. soc. chim. Romanica **1,** 3 (1919); Chem. Zentr. **1920** III, 387; Dezeine, J. pharm. Belg. **2,** 558 (1920); Chem. Zentr. **1921** I, 292. (Cited from Starkenstein.) Concerning changes on heating aqueous solutions of morphine salts see also Dietzel, Z. angew. Chem. **1928,** 1119; Dietzel and Huss, Arch. Pharm. **1928,** 641. (Cited from Trier.)

To p. 144. Morphine. When morphine is allowed to stand with $\frac{1}{10}$ *N* nitric acid for several days, small but detectable amounts of

hydrocyanic acid are formed. Jorissen, Bull. acad. roy. Belg. sciences **1910,** 224; Chem. Zentr. **1910** I, 148. (Cited from Starkenstein.)

To p. 147. Heroin. In cold 1% aqueous solution heroin is hydrolyzed in the course of several months with loss of one acetyl group. The cleavage goes further and finally results in morphine hydrochloride. Goris and Fourmont, Bull sci. pharmacol. **38,** 273 (1931); Chem. Abstr. **25,** 4086 (1931). The purification of morphine through the diacetyl derivative as practiced commercially is described by Schwyzer "Fabrikation der Alkaloide," pp. 39, 48.

To p. 149. Dihydromorphine. Preparation by dealkylation of tetrahydrothebaine with hydrobromic acid is also covered by the patent of Boehringer, D. R.-P. 504830 (Feb. 16, 1927); Wagner's Jahresber. **76,** 320 (1930).

To p. 150. Morphine salts. Busch, Centr. allgem. Path. **31,** 113 (1921), through stalagmometric measurements showed that morphine hydrochloride has no appreciable effect upon the surface tension of the water used as solvent. Eschbaum, Ber. deut. pharm. Gesell. **28,** 397 (1918), (*cf.* Traube, Berczeller and Czáki, Biochem. Zeit. **53,** 238 (1913), Berczeller and Seiner, ibid. **84,** 80 (1917)) in studies with the guttameter found that morphine solutions in the presence of small amounts of ammonia showed a changed capillarity; the morphine was thought to be in a colloidal state. (Cited from Starkenstein.)

Dox, Pharm. J. **99,** 282 (1917), has observed that if morphine sulphate is treated with the amount of sulphuric acid necessary for formation of the acid sulphate and evaporated to dryness the residue is not hygroscopic and loses no acid on extraction with anhydrous ether. It dissolves in water in the ratio of 1:1, and crystals of the neutral salt then slowly separate until the solubility (1:24) of the neutral salt is reached. The more soluble form of the sulphate is also obtained when morphine is treated with the calculated amount of $\frac{1}{10}$ *N* sulphuric acid. (Cited from Starkenstein.)

Morphine lactate was used by Irvine for the resolution of *d,l*-lactic acid; morphine *l*-lactate is much less soluble in water than the *d*-lactate. Morphine *l*-lactate cryst. in long prisms from dil. alcohol; in 5% aqueous solution $[\alpha]_D^{20} = -91.8°$. Morphine *d*-lactate cryst. in clusters of prisms and contains one molecule of hydrate-water; in 5% aqueous solution $[\alpha]_D^{20} = -92.7°$ Irvine, J. Chem. Soc. **89,** 935 (1906).

The salts of benzylmorphine with propane sulphonic acid and ethane sulphonic acid are covered by D. R.-P. 524639 (May 25, 1929) and Brit. pat. 343397 (May 24, 1929) of Chem. Fabrik vorm. Sandoz; Chem. Abstr. **25,** 4359, 5513 (1931).

To p. 171. Pseudomorphine. Abraham and Rae, Am. J. Pharm. **99,** 570 (1927), observed a change in the morphine content of opium

which was believed to be due to an oxidizing enzyme, opiase. Concerning catalytic oxidation of morphine with iron salts, see Baudisch and Davidson, J. Biol. Chem. **71,** 501 (1927). (Cited from Trier.)

Pseudomorphine takes up two molecules of hydrogen on catalytic hydrogenation, yielding tetrahydropseudomorphine. All attempts to prepare a chloro derivative of pseudomorphine with phosphorous pentachloride or thionyl chloride resulted in products containing phosphorous or sulphur. (Unpublished observations, L. F. Small and F. L. Cohen.)

To p. 176. Codeine. The isolation of naturally occurring codeine from opium, as well as the commercial procedure for the preparation of codeine by methylation of morphine with phenyltrimethylammonium hydroxide is described in detail by Schwyzer "Fabrikation der Alkaloide." The methylation of morphine with phenyltrimethylammonium hydroxide is covered by Russ. pat. 18224 (July 18, 1927); Chem. Abstr. **25,** 1038 (1931).

To p. 183. Apocodeine. The patent of Chem. Fabrik Wiernik, D. R.-P. 489185 (Wagner's Jahresber. **76** II, 318 (1930)) describes conversion of morphine alkaloids having the phenolic hydroxyl protected by alkyl groups to derivatives of the apo series with zinc chloride. Apocodeine is separated from apomorphine by the use of sparingly soluble salts, as the chromate, perchlorate, or phosphate.

To p. 185. Norcodeine. Riedel-de Haën, D. R.-P. 488610 (Wagner's Jahresber. **76** II, 318 (1930). N-Halogenalkenyl derivatives of norcodeine are prepared by treating norcodeine with γ-chloro- or bromo-allylhalogenides. γ-Chlorallylnorcodeine is a yellow powder of m. p. 54° to 56°; its hydrochloride m. at 120°, its picrate m. at 124°, its methiodide m. at 115°. γ-Bromallylnorcodeine is a colorless powder of m. p. 68° to 70°, whose picrate m. at 127°.

To p. 195. Bromocodeine. BROMOCODEINE PICRATE, cryst. from dil. alcohol, sinters at 200° and decomp. at 235°, BROMOCODEINE-N-OXIDE HYDROBROMIDE, $C_{18}H_{20}O_4NBr \cdot HBr$, prep. from codeine-N-oxide in chloroform-alcohol with a chloroform solution of bromine. It cryst. from alcohol-ether in rods, decomp. 242°. The base, BROMOCODEINE-N-OXIDE cryst. from water (with hydrate-water) and melts with decomp. at 200° to 201°. BROMOCODEINE-N-OXIDE SULPHONIC ACID occurs in two forms. The more difficultly soluble form m. at 210° to 215° (decomp.). It reduces to dihydrocodeine by the catalytic method. Karl A. T. Hill, Dissertation, Frankfurt a/M 1925.

To p. 213. β-Chlorocodide. The theoretical speculations of Schöpf and Hirsch, Ann. **489,** 224 (1931) on the acid rearrangements of morphine involve the assumption that the primary product from the action of conc. hydrochloric acid on morphine, namely β-chloromorphide, carries the chlorine atom in the 8-position. This applies also to β-chlorocodide, and is substantiated to a certain extent by

the results of hydrogenation of β-chlorocodide (p. 213, and unpublished results of Mosettig, Cohen, and Small), which behaves as though it had a double linkage in the 6,7-position and hence must have the halogen on C-8.

To p. 239. Dihydrodesoxycodeine-D. Karl A. T. Hill, Dissertation, Frankfurt a/M 1925, observed the formation of "dehydroxydihydrocodeine" on catalytic reduction of codeinone oxime hydrochloride in the presence of palladium. The PICRATE, plates of m. p. 207° and the METHIODIDE, m. p. 256° were described.

To p. 241. Tetrahydrodesoxycodeine. Goto and Sudzuki, Bull. Chem. Soc. Japan **4**, 244 (1929) have shown that Clemmensen reduction of sinomenine gives demethoxydesoxydihydrosinomenine, which is the dextrorotatory form of tetrahydrodesoxycodeine. Goto and Inaba, Bull. Chem. Soc. Japan **5**, 93 (1930), found that bromodemethoxydesoxydihydrosinomenine, having $[\alpha]_D = +40.44°$ gave with bromotetrahydrodesoxycodeine, $[\alpha]_D = -39.52°$, a racemic compound; the two substances are optical antipodes.

Desoxycodeine and tetrahydrodesoxycodeine give the diazo reaction in dilutions of 1:2,000,000 (Goto, Bull. Chem. Soc. Japan **5**, 311 (1930)).

To p. 247. Codeinone. Karl A. T. Hill, Dissertation, Frankfurt a/M 1925. Codeinone can be reduced to codeine electrolytically: Two grams of codeinone in 25 c. c. of dilute sulphuric acid were reduced on a prepared lead cathode with a current density of 9 amp. The reduction took four hours. The liquid in the cathode chamber was made alkaline with ammonia and the codeine extracted into chloroform. The conversion was also accomplished using hydrazine hydrate or sodium hydrosulphite. One gram of codeinone was boiled with aqueous sodium hydrosulphite solution; addition of ammonia precipitated codeine in the form of an oil which was obtained crystalline in quantitative yield after purification through chloroform and alcohol. Reduction of codeinone to codeine with stannous chloride, see Schöpf and Hirsch, Ann. **489**, 224 (1931).

CODEINONE-N-OXIDE (Hill, Dissertation), was prepared by the oxidation of codeinone with an equal weight of 30% hydrogen peroxide on the water bath. The oxide was precip. by addition of 50% KOH and extracted into chloroform. It is not cryst., but gives a HYDRIODIDE, $C_{18}H_{19}O_4N \cdot HI + 4H_2O$ as needles from water, m. p. 110°.

BROMOCODEINONE, from bromination of codeinone in gl. acetic acid was obtained as needles from alcohol, decomp. 192°. This compound, carrying the bromine in the aromatic nucleus is an isomer of the bromocodeinone (m. p. 156°) from bromination of thebaine, which has the bromine in ring III. —PHENYLHYDRAZONE, decomp. 172° to 190°. NITROBROMOCODEINONE, $C_{18}H_{17}O_5N_2Br$, from nitration of the bromocodeinone of Freund (Br. in ring III), prisms decomp. 210°.

To p. 248. Codeinone. It has been shown by Schöpf and Hirsch, Ann. **489**, 224 (1931), that codeinone is formed in about 7% yield

during the reduction of thebaine with stannous chloride in conc. hydrochloric acid. Codeinone appears to be much more stable to contrated hydrochloric acid than is generally supposed; at room temperature it is unchanged, and at 70° can be regained to the extent of 80%. Codeinone is reduced to the true thebainone by stannous chloride in conc. hydrochloric acid; at the same time codeine is formed. Attempts to prepare the oxime of codeinone in strong acetic acid solution or from the "red solution" of thebaine in conc. hydrochloric acid gave a product which analyzed for codeinone $+NH_2OH$. It cryst. with 1 molecule of water from alcohol, m. p. 142° to 144° (foaming), melting again at 210° to 212° with decomp.

Goto, Takubo, and Mitsui, Ann. **489**, 86 (1931), have found that when demethoxydihydrosinomenine (d-dihydrothebainone) is treated with 1 mole of bromine, the product is 1-bromodemethoxydihydrosinomenine, which shows the same melting point as 1-bromodihydrothebainone and is probably its optical antipode. When 2 moles of bromine are used, the 4,5-ether ring is closed (*cf.* p. 312) and 1-bromodimethoxydihydrosinomeneïne, the dextro form of 1-bromodihydrocodeinone, is obtained. It has the m. p. 206°, $[\alpha]_D^{23} = +161.02°$, and forms with bromodihydrocodeinone of $[\alpha]_D^{24} = -162.28°$ a racemic compound of m. p. 190.5°, optically inactive. By debromination (catalytic hydrogen) of bromodemethoxydihydrosinomeneïne, demethoxydihydrosinomeneïne can be obtained. This product has the m. p. 193° and shows $[\alpha]_D^{26} = +207.22°$. It is the *d*-form of dihydrocodeinone ($[\alpha]_D^{26} = -208.22°$) and the two substances form an inactive racemic compound of m. p. 163°. *d*-Dihydrocodeinone methiodide (m. p. 259° to 260°, decomp., $[\alpha]_D^{26} = +99.26°$) gives with *l*-dihydrocodeinone methiodide (m. p. 259° to 260°, decomp., $[\alpha]_D^{26} = -98.45°$) an inactive *d,l*-product of m. p. 268°.

To p. 249. Dihydrocodeinone. Preparation, see Boehringer Sohn, D. R.-P. 479104, Wagner's Jahresber. **75** II, 179 (1929). The identification and determination of dicodide, eucodal, and dilaudide are discussed by King, Analyst **56**, 498 (1931).

To p. 251. Pseudocodeinone. Karl A. T. Hill, Dissertation, Frankfurt a/M 1925, found that catalytic reduction of pseudocodeinone in dilute acetic acid with a palladium-black catalyst resulted in absorption of 2 molecules of hydrogen, with formation of tetrahydropseudocodeinone, $C_{18}H_{23}O_3N$. This is a phenolic base which cryst. in prisms from dil. alcohol, m. p. 145° to 147°. —Oxime, plates from dil. alcohol, m. p. 137° (decomp.), whose hydrochloride cryst. from water and decomp. at 240°.

To p. 258. Hydroxycodeinone. Karl A. T. Hill, Dissertation, Frankfurt a/M 1925. Hydroxycodeinone methiodide is converted to the hydriodide on heating with alcohol at 180° for 6 hours under pressure. Dibromobenzoylhydroxycodeinone, $C_{25}H_{21}O_5NBr_2$, cryst. in plates from dil. acetone, m. p. 216°. Anhydromonobenzoyl-7,8,14-trihydroxybromodihydrocodeinone, $C_{25}H_{22}O_6$-

NBr, prep. by benzoylation of trihydroxybromodihydrocodeinone, needles from water, m. p. 128° to 129°. Its hydrochloride cryst. in needles of m. p. 215°, having 3 molecules of crystal-water. Its phenylhydrazone hydriodide decomp. 256°, its oxime cryst. with 3 molecules of water, decomp. 244°. ANHYDROMONOBENZOYL-7,8,14-TRIHYDROXYCODEINONE, prep. by heating, 7,8,14-trihydroxycodeinone with benzoic anhydride at 150°, cryst. in prisms of m. p. 247°. DIHYDROHYDROXYCODEINONE OXIME SULPHONIC ACID, $C_{18}H_{22}O_7N_2S$, prep. by treatment of hydroxycodeinone with sodium hydrosulphite and conversion to the oxime; needles from water, not decomp. at 340°. DIHYDROHYDROXYCODEINONE SULPHONIC ACID, prep. by hydrogenation of hydroxycodeinone-N-oxide sulphonic acid; prisms from water, decomp. above 280°. DIHYDROHYDROXYCODEINONE-N-OXIDE, $C_{18}H_{21}O_5N$, cryst. from alcohol in prisms, decomp. unsharp at 210°.

To p. 261. Apomorphine. The addition of small amounts of hydrochloric acid to morphine to prevent oxidation during sterilization of solutions does not cause apomorphine formation. (Feinberg, Z. phys. Chem. **84,** 363 (1913)). Zoccola, Chem. Zentr. **1919** II, 532, finds apomorphine first detectable in 25% hydrochloric acid solution. (Cited from Starkenstein.) Apomorphine gives the diazo reaction in dilution of 1:2,000,000 (Goto, Bull. Chem. Soc. Japan **5,** 311 (1930)).

To p. 271. Dihydro-α-methylmorphimethine. Speyer and Koulen, Ber. **64,** 2815 (1931). *Cf.* Schlesinger, Dissertation, Frankfurt a/M 1929. Ozonization of des-N-methyldihydrocodeine (dihydro-α-methylmorphimethine) hydrochloride in aqueous solution yields a crystalline base, $C_{19}H_{25}O_5N$ in which nitrogen is still tertiary. The compound behaves as the ester of an aldehyde acid. It was named des-N-methyl-7,8-dihydrocodizal-3-methyl ester, and is believed to be formed through ozone rupture of the double linkage in position 2,3- of the aromatic nucleus. (*Cf.* the rupture of the 3,4-linkage in the case of dihydrocodeine and of α-chlorocodide, pp. 187, 212.) The compound forms a monoacetyl derivative and an oxime. It adds 1 molecule of hydrogen by the catalytic method. The ether bridge is opened thereby, yielding a phenol hydroxyl.

The structure assigned to des-N-methyl-7,8-dihydrocodizal-3-methyl ester represents it as containing three aliphatic double linkages; the indifference of these (especially the unsaturation in the 9,10-position) to catalytic hydrogen is surprising. According to the Speyer formulation there is no aromatic ring left in the ozonization product, so that the hydrogenation of the ether bridge can at best give an enolic hydroxyl.

Des-N-methyl-7,8-dihydrocodizal-3-methyl ester oxidizes with chromic acid to give des-N-methyl-7,8-dihydrocodizonal-3-methyl ester, in which the alcoholic hydroxyl group at C-6 has been converted to a keto group.

The course taken by the ozonolysis is believed to confirm the structure ordinarily assigned to the methylmorphimethines.

DES-N-METHYL-7,8-DIHYDROCODIZAL-3-METHYL ESTER: $C_{19}H_{25}O_5N$, cryst. from methyl alcohol, m. p. 205° to 206°, $[\alpha]_D^{18} = -101.4°$ (dil. acetic acid, C= 1.900). The base is insoluble in cold, soluble in hot alkali. —OXIME, needles, decomp. 220°. —METHIODIDE, prisms from water, decomp. above 290°. —HYDRIODIDE, rods from water, decomp. 250°. —ACETYL DERIVATIVE, isolated as the hydriodide of m. p. 234° to 235°.

DES-N-METHYL-4, 5, 7, 8-TETRAHYDROCODIZAL-3-METHYL ESTER: $C_{19}H_{27}O_5N$, 6-sided leaflets from a mixture of absol. alcohol and petroleum ether, m. p. 175° to 176°. Soluble in water and in 50% KOH; from the latter it is precip. crystalline by ammonium chloride. $[\alpha]_D^{18} = -56.8°$ (dil. acetic acid, C= 1.129).

DES-N-METHYL-7, 8-DIHYDROCODIZONAL-3-METHYL ESTER: $C_{19}H_{23}O_5N$, from oxidation of the ozonolysis product with chromic acid. It cryst. in leaflets from methanol with petroleum ether, m. p. 172°, $[\alpha]_D^{18} = -181°$ (dil. acetic acid, C= 1.030). Its HYDROCHLORIDE decomp. from 260° up.

To p. 283. Morphol. The prep. of morphol or morpholquinone in satisfactory yield from 3-phenanthrol is further described by Fieser, Ber. **64,** 701 (1931).

To p. 302. Tetrahydrothebaine. The prep. of tetrahydrothebaine by catalytic hydrogenation with platinum oxide at a suitable hydrogen ion concentration is further covered by D. R.-P. 503924 (Wagner's Jahresber. **76** II, 319 (1930)) of Boehringer Sohn.

To p. 311. Thebainone. Schöpf and Hirsch, Ann. **489,** 224 (1931) have found that the true thebainone (Formula I, p. 310) is formed together with metathebainone (thebainone, Pschorr nomenclature, which was retained throughout the thebainone chapter) during the reduction of thebaine with stannous chloride in hydrochloric acid. With the discovery of the true thebainone, in which the ethanamine chain undoubtedly occupies the same position as in thebaine, the Schöpf conception of the structure of metathebainone receives very convincing support.

The true thebainone may likewise be prepared from codeinone by treatment with stannous chloride and conc. hydrochloric acid at 70°, a reaction analogous to the formation of hydroxythebainone from hydroxycodeinone (p. 257). The reductive scission of the codeinone 4, 5-ether bridge to the true thebainone proceeds under these conditions faster than the acid rearrangement of codeinone to metathebainone, so that very little of the last named substance is found among the reaction products. When thebaine is reduced with stannous chloride in conc. hydrochloric acid under like conditions, a yield of the true thebainone as high as 50% can be obtained.

The constitution of the thebainone here described is shown by its conversion to dihydrothebainone (Formula II, p. 310) by addition of 1 molecule of hydrogen in the presence of palladium. The structure of dihydrothebainone is certain from its relationship to dihydrocodeinone (p. 248) whose structure has been so convincingly demonstrated by Schöpf (Ann. **452,** 211 (1927), p. 249 of this monograph). The position of the hydroaromatic double linkage, conjugated with the carbonyl group, is proved by the behavior of the oxime of the true thebainone on catalytic hydrogenation. Two molecules of hydrogen are absorbed and the compound is converted with loss of ammonia to dihydrothebainone. The oxime of

hydroxythebainone reduces in a similar manner (p. 258), which was recognized by Speyer (Ann. **430,** 16 (1923)) as characteristic of the oximes of α, β-unsaturated ketones.

Thebainone methiodide undergoes the morphol scission when heated to 180° with acetic anhydride. The nonbasic portion appears as the triacetyl derivative of 3, 4, 6-trihydroxyphenanthrene. Surprising in this degradation is the demethylation of C-3, and the fact that the oxygen atom at C-6 is retained in the end-product (*cf.* behavior of metathebainone in the parallel degradation). The true thebainone apparently is different from the isomeric "sulphur-free ketone" described by Pschorr (p. 230) which is quite similar in properties.

THEBAINONE: $C_{18}H_{21}O_3N+\frac{1}{2}H_2O$. The true thebainone was prepared by heating thebaine in conc. hydrochloric acid with stannous chloride at 70° for 15 minutes. It was separated from the accompanying metathebainone through its solubility in methanol. It cryst. from 96% alcohol in colorless needles of m. p. 151° to 152°. The water of crystallization is lost at 100° in vacuum. —HYDRIODIDE, needles from water, m. p. 258° to 259°. —METHIODIDE, colorless needles from 96% alcohol, m. p. 223°. —OXIME ($+\frac{1}{2}H_2O$), cryst. from dilute alcohol, m. p. 185° to 186°. Its hydrochloride cryst. in colorless needles from water, m. p. 290° to 291° (Schöpf and Hirsch, Ann. **489,** 224 (1931)).

Goto and Sudzuki, Bull. Chem. Soc. Japan **4,** 244 (1929), showed that sodium amalgam reduction of dihydrosinomenine yielded the optical antipode of dihydrothebainone.

Dihydrothebainone and metathebainone show the diazo reaction in dilution of 1:2,000,000. This appears to be a characteristic of phenanthrene alkaloids having a phenolic group at C-4 and the para position to it free. (Goto, Bull. Chem. Soc. Japan **5,** 311 (1930); ibid. **4,** 103 (1929)).

Reduction of dihydrosinomenine with sodium amalgam gives among other products demethoxydihydrosinomenol, $C_{18}H_{25}O_3N+\frac{1}{2}H_2O$, m. p. 138°, $[\alpha]_D^{23}=+45.08°$, which is the optical antipode of the dihydrothebainol of Speyer and Siebert. (Ochiai and Hakozaki, J. Pharm. Soc. Japan **50,** 360 (1930).)

Thebenone. Goto, Inaba and Shishido, Ann. **485,** 247 (1931). Degradation of the methiodide of demethoxydihydrosinomenine (*d*-dihydrothebainone) leads to a des-N-methyl base which is the optical antipode of des-N-methyldihydrothebainone (p. 318). Further degradation of the methiodide of the des-N-methyl base with alkali yielded a nitrogen-free substance, $C_{17}H_{18}O_3$, which was named *l*-dehydrothebenone, since it could be converted to *l*-thebenone by catalytic hydrogenation.

When des-N-methyldemethoxydihydrosinomenine was hydrogenated (palladium), the optical antipode of the dihydro-des-N-methyldihydrothebainone of Wieland and Kotake (p. 318) was obtained. This hydrogenation product could also be degraded to *l*-thebenone. Rotatory power of *d*-thebenone, Munster, Helv. Chem. Acta **13,** 1046 (1930).

Ozonization of dihydrohydroxythebainone methyl ether in dilute formic acid gave a product $C_{19}H_{25}O_6N$ which cryst. from alcohol in

leaflets of m. p. 124° to 125°, yield 7%. (Hill, Dissertation, Frankfurt a/M 1925.)

To p. 321. Methebenine is formed in 59% yield when thebaine is treated with stannous chloride in gl. acetic acid. The stannous chloride acts on thebaine fundamentally as does dilute hydrochloric acid, but the methoxyl group of thebaine shifts from C-6 to C-8 without hydrolysis. (Schöpf and Hirsch, Ann. **489,** 224 (1931)).

To p. 331. Morphothebaine. Kondo and Sanada, J. Pharm. Soc. Japan **51,** 509 (1931); Chem. Abst. **25,** 4887 (1931), find that methylpseudoepistephanine methiodide is the optical antipode of dimethylmorphothebaine methiodide.

Morphothebaine gives the diazo reaction in a dilution of 1:2,000,000 (Goto, Bull. Chem. Soc. Japan **5,** 311 (1930)).

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